

First Seizures, Acute Repetitive Seizures, and Status Epilepticus

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ABSTRACT

OBJECTIVE: This article provides current evidence on how and when to treat unprovoked first seizures in children and adults, guides intervention with appropriate doses and types of modern and effective therapies for acute repetitive (cluster) seizures, and reviews evidence for the diagnosis and management of established, refractory and super-refractory status epilepticus.

LATEST DEVELOPMENTS: Artificial intelligence shows promise as a clinical assistant in decision making after a first seizure. For nonanoxic convulsive refractory status epilepticus third-phase treatment, equipoise exists regarding whether it is better to add a second IV nonsedating antiseizure medication given via loading dose (eg, brivaracetam, lacosamide, levetiracetam, fosphenytoin or valproic acid) or to start an anesthetizing continuous IV infusion antiseizure medication such as ketamine, midazolam, propofol or pentobarbital.

ESSENTIAL POINTS: After a first seizure, the risk of a second seizure is about 36% at 2 years and 46% after 5 years. The risk is doubled in the presence of EEG epileptiform discharges, a brain imaging abnormality, a nocturnal first seizure, or prior brain trauma. For acute repetitive seizures, providers should give a proper dose of benzodiazepines based on the patient's weight and needs. First-phase treatment for convulsive established status epilepticus is the immediate administration of full doses of benzodiazepines. Second-phase treatment for convulsive established status epilepticus is a full loading dose of IV fosphenytoin, levetiracetam, valproic acid, or if necessary, phenobarbital.

INTRODUCTION

Emergency treatment may be necessary after a person's first seizure or at the onset of abnormal acute repetitive (cluster) seizures. It is required for status epilepticus. These emergencies can arise at home, in public, or in health care settings and can lead to serious complications, including death. Treatment for these emergencies is dictated by myriad clinical factors and informed by national and international published guidance as well as emerging research.¹⁻⁶ All diagnostic tests and treatments mentioned in this article may not be available in all areas of the world.

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RELATIONSHIP DISCLOSURE:

Dr Vossler has received personal compensation in the range of \$0 to \$499 for serving as a consultant for Biohaven Ltd; in the range of \$500 to \$4999 for serving as a consultant for Biocodex, serving on a scientific advisory or data safety
Continued on page 124

UNLABELED USE OF PRODUCTS/INVESTIGATIONAL USE DISCLOSURE:

Dr Vossler discusses the unlabeled use of adrenocorticotrophic hormone, brivaracetam, diazepam, fosphenytoin, intravenous immunoglobulin (IVIg), ketamine, lacosamide, levetiracetam, lorazepam, magnesium sulfate, methylprednisolone succinate, midazolam, pentobarbital, phenobarbital, propofol, pyridoxine, and valproic acid for first seizures, acute repetitive seizures, and status epilepticus.

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FIRST SEIZURE

Most first seizures are self-limited and produce no injury or obvious lasting effects. Nevertheless, physical injuries do occur. The risk of death is twofold to threefold that of matched controls,⁷ and a seizure with altered awareness requires restriction of driving privileges. In an early study of 407 children with a first seizure, the cumulative risk of a second seizure was 29%, 37%, 43%, and 46% at 1, 2, 5, and 10 years, respectively.^{8,9} Following a second seizure, the cumulative risk of a third seizure was 57%, 63%, and 71% at 1, 2, and 5 years, respectively.⁹ The first seizure was found to last 5 minutes or longer in 50% of patients and 30 minutes or longer (ie, status epilepticus) in 12%.¹⁰ These various risks require providers to discuss with patients the pros and cons of prescribing an antiseizure medication after the first seizure.

Treatment

The decision of whether to treat a first recognized, unprovoked seizure with an antiseizure medication was for decades incompletely informed by medical literature. A small 1989 Canadian randomized trial in children with an unprovoked, nonfebrile focal seizure or generalized tonic-clonic seizure reported that carbamazepine was effective in reducing the risk of seizure relapse.¹¹ In 1993 the First Seizure Trial Group in Italy published a randomized trial of treatment of an initial, unprovoked tonic-clonic seizure in 397 children and adults.¹² This unblinded, uncontrolled trial randomized patients either to the common antiseizure medications in use at that time (carbamazepine, phenytoin, phenobarbital, or sodium valproate) or to no antiseizure medication. The 2-year risk of seizure recurrence was 25% in treated and 51% in untreated patients (hazard ratio = 2.8). Age and EEG findings affected the chance of recurrence. Children younger than 16 years had a twofold higher risk, and the presence of epileptiform discharges increased the risk by 1.7-fold.¹² A 1996 study performed in Israel on 91 adults with a first unprovoked generalized tonic-clonic seizure found that treatment with an antiseizure medication resulted in a significant, threefold reduction of the risk of seizure recurrence after 36 months.¹³

CHILDREN. The evaluation and treatment of children with a first seizure was the subject of the 2000 American Academy of Neurology (AAN), American Epilepsy Society, and Child Neurology Society practice parameters and the 2003 AAN and Child Neurology Society practice parameters, respectively.^{14,15} The 2003 parameter concluded that after a first nonfebrile unprovoked seizure, the risk of a second seizure ranged from 14% to 65% by 1 year and increased over subsequent years, that multiple recurrent seizures occurred over time in a minority of children, and that the risk of recurrence was greater in children with a prior identifiable brain condition or epileptiform discharges on EEG. It also determined that antiseizure medication treatment appeared to decrease the risk of a second seizure, but there were little data from studies involving only children, and there was no evidence that medication improved the chance of long-term seizure remission. The parameter noted that the older antiseizure medications available at that time conveyed a risk of adverse effects that were especially important to consider for children.¹⁵

ADULTS. For antiseizure medication treatment of an adult with a first unprovoked seizure, a guideline was published jointly by the AAN and the American Epilepsy

Society in 2015.¹⁶ The guideline's systematic review identified 47 research articles that were relevant and acceptable. Like the findings of the older practice parameter for children, several conclusions were reached. The seizure recurrence risk is greatest early, within the first 2 years after the first seizure (21% to 45%). The risk of a second seizure is doubled if an adult has evidence of a previous brain insult, an EEG with epileptiform abnormalities, a significant (potentially epileptogenic) brain-imaging abnormality, or a nocturnal seizure.¹⁶ The guideline further states that immediate antiseizure medication treatment, compared with a delay of therapy pending a second seizure, is likely to reduce recurrence risk within the first 2 years but may not improve quality of life. Over a longer term (longer than 3 years), immediate antiseizure medication treatment is unlikely to improve prognosis as measured by sustained seizure remission.¹⁶

The guideline recommended that adults should be advised that the risk of antiseizure medication adverse events may range from 7% to 31% and that these are likely predominantly mild and reversible.¹⁶ That degree of risk of adverse events is high and likely no longer correct because in the five studies that were analyzed to assess the risk of adverse effects 1570/1589 (99%) of patients used the oldest antiseizure medications: carbamazepine, phenobarbital, phenytoin, and divalproex.^{12,13,17-19} These drugs are no longer frequently used in high-income countries, largely because they are well known to have both a greater risk of side effects and more pharmacokinetic drug interactions than modern antiseizure medications such as lamotrigine, levetiracetam, and lacosamide.

The guideline stressed that a provider's recommendations on whether to start immediate antiseizure medication treatment after a first seizure should be based on individualized assessments that weigh the risk of recurrence against the adverse effects of antiseizure medication therapy and that providers should both consider the preferences of educated patients and advise patients that immediate treatment will reduce the seizure risk over the next 2 years but will not improve the long-term prognosis for seizure remission.¹⁶

New Research

Lawn and colleagues found that a first seizure occurring during sleep, without either epileptiform abnormalities in the EEG or evidence of a remote symptomatic cause, approximately doubled the risk of a subsequent seizure in adults.²⁰ After a first seizure during sleep, recurrences mostly occurred during sleep.²⁰ Pang and colleagues studied 1278 patients with a first, unprovoked seizure compared with 2556 matched controls over a mean greater than 7 years and found an overall hazard ratio of 3.06 for death in the years after a first seizure, equivalent to approximately 10 years of potential life lost.⁷ As anticipated, an underlying neurologic cause of the seizure was a strong risk factor for death; however, a first seizure of an unknown cause still carried a greater risk of mortality. Interestingly, a second seizure was not a significant risk factor for death, and antiseizure medication treatment was not associated with a reduction in the risk of mortality.⁷

Neurophysiologic and neuroimaging tests are important data used in diagnostic and treatment decision making after first seizures. Several studies have shown that MRI is superior to CT in the setting of first seizures, revealing an epileptogenic cerebral lesion in about one-fourth of patients. More advanced neurophysiologic tests such as 24-hour ambulatory EEG or video-EEG monitoring has been shown to lead to a more precise diagnosis of a first seizure

KEY POINTS

- Seizure recurrence risk is greatest early, within the first 2 years after the first seizure (21% to 45%). The risk of a second seizure is doubled if an adult has evidence of a previous brain insult, an EEG with epileptiform abnormalities, a significant (potentially epileptogenic) brain-imaging abnormality, or a nocturnal seizure.
- A large study of patients with a first, unprovoked seizure found an overall hazard ratio of 3.06 for death in the years after a first seizure, equivalent to approximately 10 years of potential life lost.

and to the ability to diagnose new-onset epilepsy.²¹ In some regions of the world, advanced testing is not available, and a cost-benefit analysis of such testing is needed.

Novel research on first seizures used the Markov decision model, a type of artificial intelligence that is used for modeling decision making in a complex system.²² It simulated a clinical trial to study whether immediate antiseizure medication treatment or deferred medication would maximize the overall quality-adjusted life years of a patient, depending on different features of hypothetical cases.²² The analysis favored immediate antiseizure medication treatment in two of three scenarios.²² This Markov decision model mathematical framework required making a few assumptions. It can be argued that the researchers should have used both the 46% 5-year seizure recurrence risk calculated in the adult guideline¹⁶ (rather than the 60% figure used) and a lower percentage risk of antiseizure medication side effects than in the guideline, given that the newer drugs have adverse effects in fewer patients than the oldest antiseizure medications. Nevertheless, even if those adjustments to the Markov decision model dynamic system had been made, it appears likely that the overall conclusion would still be that immediate antiseizure medication treatment is preferable to deferred treatment in adult first-seizure patients over a wide and clinically relevant range of variables.²² The use of the Markov decision model and other forms of artificial intelligence will almost certainly assist the decision making of clinicians in the future.

ACUTE REPETITIVE SEIZURES

Acute repetitive seizures most commonly occur in the outpatient setting but do occur in some patients in a hospital setting. In the ambulatory setting, acute repetitive seizures are often called seizure clusters. A cluster may contain focal aware seizures, focal impaired awareness seizures, focal to bilateral tonic-clonic seizures, or generalized absence, myoclonic, atonic, and tonic-clonic seizures, depending upon the patient's epilepsy type. A pattern typically exists in a large percentage of patients with epilepsy in which multiple seizures are experienced over 24 hours or a few days, followed by many days without seizures or with random single seizures. This type of pattern often recurs on an infradian (multiday, or *multidien*) cycle (eg, monthly).²³ An abnormal cluster of acute repetitive seizures in epilepsy patients may also occur in response to common triggers like antiseizure medication nonadherence, intercurrent illness, sleep deprivation, use of illicit drugs or excessive alcohol use, and menstrual cycling.

Treatment of Cluster Seizures

Determining whether a patient is having an abnormal cluster of seizures that requires intervention with an antiseizure medication as opposed to the typical normal variation of their typical seizure frequency pattern may be difficult at the beginning of the acute repetitive seizures episode. Patients, caregivers, and health care providers are aided in making this distinction based on subjective experience with the historical seizure pattern, particularly when it is supplemented with objective long-term seizure calendars.²³ The determination that a patient needs antiseizure medication treatment is informed by more than just the absolute number of seizures over time. Rather, it takes into consideration the strength, severity, and type of the seizures; whether the patient recovers awareness between seizures, is febrile or ill, or is injured

by the seizures; and whether the interval between seizures is increasing or decreasing.

Cluster seizures can be treated acutely with additional doses of a patient's normal oral antiseizure medications or with oral benzodiazepines. However, the time to maximum concentration of these drugs in the plasma is approximately 60 to 90 minutes because they are absorbed in the jejunum, and this time is further delayed if they are taken shortly after a meal. In the United States, acute repetitive seizures may be treated more quickly with US Food and Drug Administration (FDA)-approved devices, including rectal diazepam using weight- and age-based dosing ranging from 2.5 mg to 20 mg, intranasal diazepam using weight- and age-based dosing ranging from 5 mg to 20 mg, intranasal midazolam 5 mg, or an intramuscular midazolam autoinjector at 10 mg. It is important that prescribers use the patient's age and weight in determining the correct dose of rescue medication because insufficient doses may not stop acute repetitive seizures thereby leading to status epilepticus. Providers are encouraged to discuss and develop in advance a written, individualized seizure rescue plan for each of their patients with epilepsy. When in doubt about the response to interventions such as those described above, caregivers should be ready to summon emergency medical services if acute repetitive seizures do not stop, if the seizures become more frequent or severe, or if they lead to injury, respiratory compromise, or a depressed level of awareness between seizures. Cluster seizures most commonly occur in patients with preexisting epilepsy, but they can occur as a first-ever unprovoked seizure. When a patient has a seizure cluster as their presenting seizure, they are at a substantially increased risk of death over subsequent years.⁷

In the hospital setting, acute repetitive seizures can be seen as electrographic (subclinical) seizure patterns in the EEGs of patients in a variety of contexts including nonconvulsive status epilepticus, hypoxic-ischemic encephalopathy, after antiseizure medication withdrawal in inpatients undergoing diagnostic video-EEG monitoring for epilepsy, and other encephalopathic states. The treatment of these acute repetitive seizures is highly dependent on etiology and antiseizure medications that the patient is already receiving.

STATUS EPILEPTICUS

Status epilepticus has been referenced in world literature for more than 3 millennia. Extensive basic and clinical research over the past four decades has provided a rich understanding of the definition, classification, and different stages of this diverse and dangerous condition.

History

The first description of status epilepticus is attributed to Esagil-kin-apli. In the *Sakikku* (all diseases) chapter 6 in Babylon between 1067 and 1046 BCE he wrote, "If the possessing demon possesses him many times during the middle watch of the night ... It may go on for some time, but he will die."²⁴ The origin of the term status epilepticus is believed to be the phrase, "L' état de mal épileptique" written in 1824 by Louis Calmiel in his *Thèse de Université de Paris*.²⁵

Definition

The current definition and classification of status epilepticus are found in the 2015 International League Against Epilepsy task force report.²⁶ The definition of *status epilepticus* is

KEY POINTS

- Twenty-four-hour ambulatory EEG or video-EEG monitoring has been shown to lead to a more precise diagnosis of a first seizure and to the ability to diagnose new-onset epilepsy, but in some regions of the world, such advanced testing is not available, and a cost-benefit analysis of such testing is needed.

- Use of the Markov decision model and other forms of artificial intelligence will likely help clinicians decide whether to prescribe an antiseizure medication to a patient who had a first-time seizure.

- Many people with epilepsy experience a pattern of clusters of seizures that occur on an infradian (multiday) cycle (eg, monthly). This phenomenon must be distinguished from acute repetitive seizures that are a departure from the patient's characteristic pattern.

- Acute repetitive seizures may occur in response to common triggers such as antiseizure medication nonadherence, intercurrent illness, sleep deprivation, use of illicit drugs or excessive alcohol use, and menstrual cycling.

- In the United States, acute repetitive seizures may be treated with rectal diazepam using weight- and age-based dosing ranging from 2.5 mg to 20 mg, intranasal diazepam using weight- and age-based dosing, ranging from 5 mg to 20 mg, intranasal midazolam 5 mg, or an intramuscular midazolam 10-mg autoinjector.

“a condition resulting either from the failure of the mechanisms responsible for seizure termination or from the initiation of mechanisms which lead to abnormally prolonged seizures (after time point t_1). It is a condition that can have long-term consequences (after time point t_2), including neuronal death, neuronal injury, and alteration of neuronal networks, depending on the type and duration of seizures. This definition is conceptual, with two operational dimensions: the first is the length of the seizure and the time point (t_1) beyond which the seizure should be regarded as ‘continuous seizure activity.’ The second time point (t_2) is the time of ongoing seizure activity after which there is a risk of long-term consequences. In the case of convulsive (tonic-clonic) SE, both time points (t_1 at 5 minutes and t_2 at 30 minutes) are based on animal experiments and clinical research.”²⁶

There is limited information to define t_1 and t_2 in focal seizures and no information for absence seizures.

Classification

The classification of status epilepticus is based on four axes: semiology (with and without prominent motor signs), etiology (known and unknown causes), EEG patterns and features, and age (neonatal, infancy, childhood, adolescence, adulthood, and old age).²⁶ A simplified classification of the common types of status epilepticus based only on the first axis, semiology, is convulsive status epilepticus, defined as overt convulsions lasting longer than 5 minutes or two or more back-to-back tonic-clonic seizures without full return of consciousness between them; nonconvulsive status epilepticus, which includes continuous absence, focal sensory, or focal impaired awareness seizures lasting 10 minutes or longer; myoclonic status epilepticus; and focal motor status epilepticus (formerly, *epilepsia partialis continua*).

Stages

The first stage is termed *developing status epilepticus*, defined as seizures leading up to status epilepticus. The second stage is *established status epilepticus*, defined as status epilepticus lasting longer than 5 minutes at which time therapy should begin. The third stage is *refractory status epilepticus*, which is continued status epilepticus due to failure of two adequately dosed antiseizure medications in different drug classes (eg, a benzodiazepine and phenytoin). *Super-refractory status epilepticus* is defined as status epilepticus persisting despite the use of anesthetizing antiseizure medications for longer than 24 hours.²⁷

Status epilepticus most commonly occurs in patients with a history of seizures but in a large study was determined to be the first seizure presentation in 20% of patients.⁷ When a first seizure is status epilepticus there is a substantially higher risk of death.⁷

Established Convulsive Status Epilepticus

In 2016 the American Epilepsy Society published its guideline on the treatment of established convulsive status epilepticus in children and adults.¹ Ratings of the levels of evidence were based on an earlier modification of the AAN Clinical Practice Guideline Process Manual.²⁸

FIRST-PHASE TREATMENT FOR ESTABLISHED CONVULSIVE STATUS EPILEPTICUS. For the first phase of treatment of established convulsive status epilepticus, bolus administration of 4 mg of IV lorazepam, 10 mg of IM midazolam, or 10 mg of IV diazepam is recommended for adults weighing more than 40 kg (88.2 lb) (TABLE 5-1). This was supported by several randomized controlled trials.²⁹⁻³² There is some evidence that lorazepam may be superior to diazepam.^{30,33} Diazepam is more lipid soluble than lorazepam, allowing its more rapid blood-brain barrier penetration, but diazepam redistributes back out of the brain into adipose tissue, resulting in a short, 2 to 4 hour, duration of effect on the brain.³⁴ Nevertheless, the guideline recommends any of the three benzodiazepines at the previously listed doses.¹

Despite recommendations to use full doses of benzodiazepines, multiple research studies have shown that the majority of children and adults with status epilepticus are underdosed in clinical practice.³⁵⁻³⁷ Even in ESETT (Established Status Epilepticus Treatment Trial), a Class I randomized controlled trial, midazolam and lorazepam doses (mostly given in the prehospital setting) were lower than guideline recommendations in more than 75% of the 460 subjects.³⁸ When patients with status epilepticus receive treatment with benzodiazepines that is less than optimal, up to three negative outcomes can occur. The first potential negative outcome is that health care providers likely prescribe lower doses of benzodiazepines under the false assumption that this may avoid respiratory depression. Uncontrolled status epilepticus is more likely than benzodiazepines to cause respiratory depression. A good example supporting this concept is from the PHTSE (Prehospital Treatment of Status Epilepticus) trial, a Class I randomized controlled trial of prehospital status epilepticus in which patients randomized to placebo had greater than 2 times the rate of respiratory dysfunction than those who received lorazepam or diazepam.³⁰

The second potential negative outcome of less-than-optimal treatment with benzodiazepines is that compared with full-dose, low-dose benzodiazepines are less effective at stopping status epilepticus. The observational SENSE (Sustained Effort Network for Treatment of Status Epilepticus) clinical registry found that benzodiazepine dosing was lower than recommended in more than 75% of adults with refractory convulsive status epilepticus and adults with nonconvulsive status epilepticus compared with patients who are nonrefractory ($P < .001$) ($n = 1049$).³⁷ In that study, the time from convulsive status epilepticus onset to first treatment was 30 minutes, the time from nonconvulsive status epilepticus onset to first treatment was 2.5 hours, and the use of benzodiazepines and higher total doses of antiseizure medications used in the first phase produced a shorter time to convulsive status epilepticus and nonconvulsive status epilepticus control.³⁷ Among the 996 patients in the SENSE registry, 545 (54.7%) progressed to refractory status epilepticus, and in treatment for these patients, there was a greater likelihood of deviation from treatment guidelines ($P < .001$).³⁹ This underdosing of benzodiazepines in the prehospital setting resulted in a need for treatment with further antiseizure medications compared with the patients receiving optimal benzodiazepine treatment.⁴⁰

The third potential negative outcome from undertreatment with benzodiazepines is that time delays in the delivery of benzodiazepines are associated with greater adverse outcomes, including death. The Pediatric Status Epilepticus Research Group has actively studied delays in treatment of status epilepticus with both benzodiazepines and nonbenzodiazepine antiseizure

KEY POINTS

- Status epilepticus as defined by the 2015 International League Against Epilepsy task force report is a condition resulting either from the failure of the mechanisms responsible for seizure termination or from the initiation of mechanisms that lead to abnormally prolonged seizures.
- The first stage of status epilepticus is *developing status epilepticus*, defined as seizures leading up to status epilepticus.
- The second stage of status epilepticus is *established status epilepticus*, defined as status epilepticus lasting longer than 5 minutes (time point t₁) at which time therapy should begin.
- The third stage of status epilepticus is *refractory status epilepticus* which is continued status epilepticus due to failure of two adequately dosed antiseizure medications in different drug classes (eg, a benzodiazepine and phenytoin). *Super-refractory status epilepticus* is defined as status epilepticus persisting despite the use of anesthetizing antiseizure medications for longer than 24 hours.
- For the first phase of treatment of established convulsive status epilepticus, bolus administration of 4 mg of IV lorazepam, 10 mg of IM midazolam, or 10 mg of IV diazepam is recommended for adults weighing more than 40 kg (88.2 lb).

medications. A Pediatric Status Epilepticus Research Group multicenter study of refractory convulsive status epilepticus found that the two-thirds of children who received delayed first-stage benzodiazepine treatment had increased odds of death and need for continuous infusion anesthetizing antiseizure medications, longer duration convulsive status epilepticus, and more frequent hypotension.⁴¹ Intermittent convulsive refractory status epilepticus and onset of convulsive refractory status epilepticus outside the hospital were found by the Pediatric Status Epilepticus Research Group to be associated with longer delays to administration of the first benzodiazepine and the first nonbenzodiazepine antiseizure medication.⁴² A 2015 Pediatric Status Epilepticus Research Group study found that in pediatric patients the first dose of a benzodiazepine and first dose of a nonbenzodiazepine antiseizure medication were given at a median of 40 and 69 minutes after the onset of status epilepticus.⁴³ Furthermore, children with refractory status epilepticus did not receive more timely treatment if they had a history of epilepsy, but a history of status epilepticus was associated with more timely administration of a rescue medication.⁴³

Quality improvement initiatives have been shown to successfully reduce the time to begin first-phase benzodiazepine treatment as well as second-phase antiseizure medication administration.^{44,45}

SECOND-PHASE TREATMENT FOR ESTABLISHED CONVULSIVE STATUS EPILEPTICUS. For the second phase of treatment of convulsive established status epilepticus, IV loading doses of fosphenytoin 20 mg phenytoin equivalents/kg, valproic acid

TABLE 5-1

American Epilepsy Society Guideline for Convulsive Established Status Epilepticus^a

First phase

IM midazolam 10 mg for more than 40 kg (88.2 lb) (5 mg for 13 kg [28.6 lb] to 40 kg [88.2 lb]) single dose (highly likely effective), or

IV lorazepam 0.1 mg/kg/dose, maximum: 4 mg/dose, may repeat dose once (highly likely effective), or

IV diazepam 0.15 mg to 0.2 mg/kg/dose, maximum is 10 mg/dose, may repeat dose once (highly likely effective)

or if none of the above is available, give

IV phenobarbital 15 mg/kg in a single dose (highly likely effective), or rectal diazepam 0.2-0.5 mg/kg, max 20-mg single dose (likely effective), or nasal or buccal midazolam (likely effective)

Second phase

IV fosphenytoin (20 mg phenytoin equivalents/kg, max 1500 mg PE, single dose up to 150 mg/min [insufficient evidence]) (also available intramuscularly), or

IV valproic acid (40 mg/kg, maximum 3000 mg, single dose [likely effective]), or

IV levetiracetam (60 mg/kg, maximum 4500 mg, single dose, [insufficient evidence])

or if none of the above is available, give

IV phenobarbital 15 mg/kg, single dose (likely effective)

^a Data from Glauser T, et al, *Epilepsy Curr.*¹

40 mg/kg, or levetiracetam 60 mg/kg are recommended for children and adults (TABLE 5-1).¹ Since the publication of the American Epilepsy Society Guideline, additional studies have been conducted. The ESETT study examined 384 patients aged 1 to 95 years with benzodiazepine-resistant established convulsive status epilepticus.⁴⁶ Treatment was IV loading doses of either fosphenytoin 20 mg phenytoin equivalents/kg, levetiracetam 60 mg/kg, or valproic acid 40 mg/kg. Cessation of convulsive status epilepticus was seen in equal proportions with levetiracetam (47%), fosphenytoin (45%), and valproic acid (46%) (not significant) (likely effective). No differences in level of consciousness or major safety events occurred.

The Class I SAMUKeppra (Prehospital Treatment With Levetiracetam Plus Clonazepam in Status Epilepticus) study showed that the initial clonazepam 1-mg to 2-mg IV dose controlled prehospital convulsive status epilepticus equally well in adults subsequently given either placebo or levetiracetam 2500 mg.⁴⁷ A Class II study of adults older than 60 years found that after initial 4-mg to 6-mg lorazepam doses, control of convulsive status epilepticus was no different between IV loading doses of levetiracetam at 20 mg/kg to 25 mg/kg and valproic acid at 20 mg/kg to 25 mg/kg.⁴⁸

Two Class III open-label randomized controlled trials were completed in children with established convulsive status epilepticus. The EcLiPSE (Levetiracetam Versus Phenytoin for Second-line Treatment of Paediatric Convulsive Status Epilepticus) and ConSEPT (Levetiracetam Versus Phenytoin for Second-line Treatment of Convulsive Status Epilepticus in Children) studies found that IV loads of levetiracetam 40 mg/kg and phenytoin 20 mg/kg are possibly equally effective in terminating convulsive status epilepticus in children.^{49,50} Other smaller studies on the second-phase treatment of children and adults with convulsive status epilepticus have been completed.⁵¹⁻⁵³ Taken together, the newer ESETT trial in adults and children, two large Class II randomized controlled trials in adults, the EcLiPSE and ConSEPT (Class III) open-label studies in children, and others revealed no consistent, major differences between IV loading doses of levetiracetam, phenytoin, fosphenytoin, and valproic acid in controlling established convulsive status epilepticus. These findings appear to support the 2016 American Epilepsy Society Guideline.¹

REFRACTORY CONVULSIVE STATUS EPILEPTICUS. Among adults with convulsive status epilepticus, a US Department of Veterans Affairs trial showed that the first antiseizure medication worked in 55.5%, the second antiseizure medication worked in another 7.0%, and the third antiseizure medication worked in only 2.3% of patients.³¹ In children, the second antiseizure medication appears less effective than the first, and there are no data about the third antiseizure medication.¹ After failure to stop status epilepticus with a second appropriately selected and dosed antiseizure medication, refractory status epilepticus is diagnosed.

Refractory status epilepticus develops in approximately 23% to 55% of patients with status epilepticus, causes death in 15% to 39% of adults (a lower rate in children), and leads to a return to baseline neurologic status in a minority of patients, longer hospital stays, and a need for rehabilitation in many patients.^{39,54-59} A very large (6,818 children and 26,996 adults) nationwide study of new-onset status epilepticus in Korea determined that 30-day and 1-year mortalities were 1.8% and 4.6%, respectively, for children and 10.2% and 30.3%, respectively, for

KEY POINTS

- Despite recommendations to use full doses of benzodiazepines, most children and adults with status epilepticus are underdosed in clinical practice.

- Uncontrolled status epilepticus is more likely than benzodiazepines to cause respiratory depression.

- For the second phase of treatment of convulsive established status epilepticus, IV loading doses of fosphenytoin 20 phenytoin equivalents/kg, valproic acid 40 mg/kg, or levetiracetam 60 mg/kg are recommended for children and adults.

- Class I randomized controlled trials in refractory status epilepticus comparing both the efficacy and the adverse effects of treatment with an anesthetizing continuous-infusion antiseizure medication versus a second nonanesthetizing antiseizure medication have not been done.

- A nationwide study of new-onset status epilepticus in Korea determined that 30-day and 1-year mortalities were 1.8% and 4.6%, respectively, for children and 10.2% and 30.3%, respectively, for adults. New neurologic disabilities occurred in 10.7% of all patients, but children aged 5 to 9 years had the highest risk of disability (21.3%).

adults.⁶⁰ The study included all potential etiologies of status epilepticus, with only 5% attributed to anoxic and hypoxic brain injury. Of the 33,814 patients, 33.2% of children and 17.6% of adults progressed to refractory status epilepticus requiring IV anesthetizing antiseizure medication infusions. New neurologic disabilities occurred in 10.7% of all patients, but children aged 5 to 9 years had the highest risk of disability (21.3%).⁶⁰ Epilepsy that was new and treatment-resistant occurred in 0.8% overall.⁶⁰ Factors predictive of mortality in children and adults were old age, presence of acute etiology, and refractory status epilepticus.⁶⁰

It is important to note that status epilepticus, refractory status epilepticus, and nonconvulsive status epilepticus following cardiac arrest are well-known to be treatment resistant, have been excluded from almost all treatment studies, and are therefore not considered in this article.

THIRD-PHASE TREATMENT FOR REFRACTORY CONVULSIVE STATUS EPILEPTICUS. For the third-phase treatment of convulsive status epilepticus (ie, if established status epilepticus is not stopped with a benzodiazepine followed by a single nonanesthetizing antiseizure medication), clinicians often choose continuous infusions of anesthetizing antiseizure medications (continuous IV infusion antiseizure medications) such as midazolam, pentobarbital, or propofol instead of an additional largely nonsedating antiseizure medication. This practice is based on expert opinion that rapid control of convulsive status epilepticus is essential to prevent brain injury, but Class I randomized controlled trials comparing the efficacy and the potentially serious adverse effects of continuous IV infusion antiseizure medications² with the efficacy and adverse effects associated with treatment using a second nonanesthetizing antiseizure medication have not been performed.¹

Some retrospective, observational studies were performed that address this question. A Class III study found that the use of continuous IV infusion antiseizure medications was associated with a threefold increased risk of death and fourfold increased incidence of infection, even when correcting for age and status epilepticus severity.⁶¹ Another Class III study of continuous IV infusion antiseizure medications found a sevenfold relative increased risk of new disability, a ninefold increased risk of death, a fourfold increased risk of infection, and prolongation of hospital stays by one week.⁶² A large Class III study found that the use of anesthetic continuous IV infusion antiseizure medications (so called, therapeutic coma) was much more common at three affiliated Boston hospitals than at a Swiss center.⁶³ In that study, therapeutic coma was associated with longer hospitalizations, but not with increased mortality, and was more commonly used in patients with refractory status epilepticus, higher Status Epilepticus Severity Scores (TABLE 5-2⁶⁴), and younger age.⁶³ In contrast, two retrospective observational studies reported that shorter duration, yet deeper, therapeutic coma was associated with fewer in-hospital complications and fewer poor outcomes.^{65,66} A 2024 study analyzing patients treated at a Swiss hospital between 2011 and 2019 found that the doses of continuous IV infusion antiseizure medications had to be increased in 57% of 111 adults with refractory status epilepticus.⁶⁷ Even though subjects with anesthetic dose escalation had higher morbidity than those without continuous IV infusion antiseizure medication dose increases, they had decreased odds of in-hospital death, and the survivors had similar functional outcomes.⁶⁷ These retrospective studies provide conflicting data on the adverse effects

of anesthetizing continuous IV infusion antiseizure medications. A 2024 systematic review concluded that the data from the included studies were so heterogeneous that no definitive conclusion could be reached on the choice of optimal first continuous IV infusion antiseizure medication in the treatment of refractory status epilepticus.⁶⁸

Novy and colleagues reported that escalating treatment with a nonsedating antiseizure medication terminated refractory status epilepticus in more than one-half of their patients.⁵⁸ Similarly, a Class III study of lorazepam followed by phenytoin, levetiracetam, and valproic acid for convulsive status epilepticus found that by the time all three were used sequentially, status epilepticus was controlled in 92% of patients, thereby avoiding the need for anesthetizing antiseizure medications.⁵⁶ In the SENSE registry,³⁷ 287 of 545 (52.7%) patients with refractory status epilepticus had good outcomes (modified Rankin scale score 2 or lower or unchanged), which correlated with lower status epilepticus severity, lack of intubation, adequate first-phase benzodiazepine dose,^{1,46} absence of acute etiology, and shorter durations of status epilepticus and hospitalization (all $P < .001$).³⁹ Note that in the SENSE registry, the doses for levetiracetam, phenytoin, and valproic acid were all lower than in the American Epilepsy Society Guideline and the ESETT study. These three studies suggest that anesthetizing continuous IV infusion antiseizure medications could be avoided in favor of another nonsedating antiseizure medication in most patients, especially when guidelines for dosing and timing of first-phase and second-phase treatments are followed. A caveat is that the results of these retrospective studies must be interpreted cautiously because selection bias may have compromised the findings. Patients receiving anesthetizing continuous IV infusion antiseizure medications may have been more ill, those patients may have had more refractory convulsive status epilepticus, and many research case series do not control for antiseizure medication timing and dosing.²

Status Epilepticus Severity Score^a

TABLE 5-2

Predictors	Features	Score ^b
Consciousness	Alert, somnolent, or confused	0
	Stupor or coma	1
Worst status epilepticus seizure type	Focal aware, focal impaired awareness, absence, or myoclonic	0
	Tonic-clonic convulsive	1
	Nonconvulsive status epilepticus in coma	2
Age	Younger than 65 years	0
	65 years or older	2
History of prior seizures	Yes	0
	No or unknown	1

^a Modified with permission from Rosetti AO, et al, J Neurol.⁶⁴ © 2008 Springer Nature.

^b Score totals can range from 0 to 6. A favorable score is 0 to 2.

In the past several years additional nonsedating IV antiseizure medications (lacosamide, levetiracetam, and valproic acid) have become available in many countries and are used in place of phenytoin and phenobarbital to treat refractory status epilepticus. A strategy of using a second nonsedating IV antiseizure medication after failure of a second-phase nonsedating drug may avoid the complications of a long intensive care unit stay associated with anesthetizing continuous IV infusion antiseizure medications.

As guidance for the treatment of refractory status epilepticus, the American Epilepsy Society published Treatment of Refractory Convulsive Status Epilepticus: A Comprehensive Review by the American Epilepsy Society Treatments Committee.² It determined that lacosamide is possibly effective but that insufficient evidence of efficacy existed for other IV antiseizure medications, including brivaracetam, ketamine, levetiracetam, midazolam, pentobarbital (thiopental, in Europe), phenytoin, propofol, and valproic acid in the treatment of convulsive refractory status epilepticus.² Also, evidence was mixed regarding whether a second nonsedating antiseizure medication should be used or whether it is optimal to move directly to a continuous infusion of an anesthetizing antiseizure medication after the failure of second-phase medication.^{2,66,69} Therefore, there is no consensus on whether therapeutic coma with a continuous IV infusion antiseizure medication should be initiated immediately after failure of a benzodiazepine and a nonsedating antiseizure medication or whether a second nonanesthetizing antiseizure medication should be tried first.⁶³

Since the publication of the American Epilepsy Society's comprehensive review on convulsive refractory status epilepticus, a newer study in adults in high-income versus low–middle-income countries found that midazolam and propofol infusions had equally good outcomes.⁷⁰ Also, a newer study on ketamine for refractory status epilepticus in neonates and children at a university pediatric hospital showed efficacy in three-fourths of cases.⁷¹ A 2024 systematic review and meta-analysis of ketamine in pediatric refractory status epilepticus is available.⁷²

SUMMARY OF TREATMENT FOR CONVULSIVE STATUS EPILEPTICUS. Prompt first-phase treatment of convulsive status epilepticus should include full doses of an IV or IM benzodiazepine followed quickly by a full loading dose of IV levetiracetam, phenytoin, or valproic acid (or if none of these are available, phenobarbital) in the second phase as shown in **TABLE 5-1**.¹ Furthermore, for refractory convulsive status epilepticus, the third-phase antiseizure medication could include IV brivaracetam, ketamine, lacosamide, levetiracetam, midazolam, pentobarbital (thiopental, in Europe), phenytoin, propofol, or valproic acid based on the clinical situation, first nonsedating antiseizure medication used, drug and intubation availability, and the health care provider's experience and comfort using these nonsedating or anesthetizing antiseizure medications.² Pharmacologic information on these antiseizure medications, and others used for the special situations of infancy, pregnancy, and super-refractory status epilepticus (adrenocorticotrophic hormone, intravenous immunoglobulin [IVIg], magnesium sulfate, methylprednisolone, and pyridoxine), are shown in **TABLE 5-3**.

Nonconvulsive Status Epilepticus

Convulsive status epilepticus is generally readily recognized in prehospital and emergency department settings, but nonconvulsive status epilepticus is

very difficult to diagnose in many patients. For example, Swiss investigators found that nonconvulsive status epilepticus is frequently missed, especially in elderly patients and those with no history of epilepsy.⁷³ They found that independent predictors for not receiving benzodiazepines were increasing age and higher Glasgow Coma Scale scores.⁷³ Furthermore, a missed diagnosis of nonconvulsive status epilepticus was independently associated with high odds for no return to functional baseline in survivors (odds ratio 3.83, $P=.021$).⁷³ The clinical diagnosis of nonconvulsive status epilepticus without motor signs requires a high index of suspicion and urgent video-EEG monitoring.

Types of nonconvulsive status epilepticus include focal aware sensory, focal aware motor, focal impaired awareness, and absence status epilepticus, as well as nonconvulsive status epilepticus associated with aphasia, depressed level of consciousness, or coma. In the SENSE registry, 457 patients had convulsive status epilepticus and 592 had nonconvulsive status epilepticus (including nonconvulsive status epilepticus in coma, focal aware status epilepticus, focal unaware status epilepticus, and absence status epilepticus).³⁷ The patients with nonconvulsive status epilepticus had a median age of 72 years, a baseline modified Rankin score of 0–2 in 45%, a Status Epilepticus Severity Score of 2 or less in 55%, and in-hospital mortality of 19%. The median latency to the first-phase treatment was 30 minutes for convulsive status epilepticus but was 150 minutes for nonconvulsive status epilepticus, likely owing to delayed diagnosis of the latter. Bolus dosing of first-phase benzodiazepines was lower than guideline recommendations in 78% of patients with nonconvulsive status epilepticus.³⁷ Benzodiazepine dosing was even lower in the patients with nonconvulsive status epilepticus who went on to develop refractory as opposed to controlled nonconvulsive status epilepticus, suggesting that refractoriness was due to the very low benzodiazepine doses. Factors associated with shorter time to status epilepticus cessation within the first 12 hours were lower Status Epilepticus Severity Score, fewer comorbidities, use of a benzodiazepine as first-phase treatment, and higher cumulative standard antiseizure medication doses within the first hour.³⁷ Mortality is high in patients with nonconvulsive status epilepticus. A US study of 100 consecutive patients with nonconvulsive status epilepticus found that 18 died.⁷⁴ In that study, mortality was associated with nonconvulsive status epilepticus due to an acute medical cause, severe mental status impairment, and development of acute complications, but it was not associated with the type of EEG ictal discharge.⁷⁴

The treatment of nonconvulsive status epilepticus is not driven by guidelines; rather it is informed by individual patient circumstances (**CASE 5-1**). Many patients with nonconvulsive status epilepticus have been treated with both nonsedating and continuous IV infusion antiseizure medications and have progressed to super-refractory status epilepticus. In those cases, patient demographics, etiology (eg, postanoxic), neurologic examination findings, underlying seizure type, evolving EEG patterns, neuroimaging abnormalities, antiseizure medications tried, comorbidities, patient and family wishes, and other factors all influence which antiseizure medications and other treatments the health care team might select next.

New-Onset Refractory Status Epilepticus

New-onset refractory status epilepticus (NORSE), an uncommon form of refractory status epilepticus, occurs in children and adults.^{75–77} In a Pediatric

KEY POINTS

- For refractory convulsive status epilepticus, the third-phase antiseizure medication could include IV brivaracetam, ketamine, lacosamide, levetiracetam, midazolam, pentobarbital (thiopental, in Europe), phenytoin, propofol, or valproic acid.

- A missed diagnosis of nonconvulsive status epilepticus is associated with an odds ratio of 3.83 for no return to functional baseline in survivors. The clinical diagnosis of nonconvulsive status epilepticus without motor signs requires a high index of suspicion and urgent video-EEG monitoring.

Status Epilepticus Research Group study of children with refractory status epilepticus, only 16% had NORSE.⁷⁸ In a study of adults with refractory status epilepticus, only 10.7% had NORSE, of whom 26 of 27 had new-onset super-refractory status epilepticus.⁷⁹ *NORSE* is defined as a clinical presentation, not a specific diagnosis, occurring in patients without active epilepsy or other preexisting relevant neurologic disorders with new onset of refractory status epilepticus without a clear acute or active structural toxic or metabolic cause.⁷⁶ Febrile infection-related epilepsy syndrome (FIRES), a subcategory of NORSE, is applicable to patients of all ages and requires a prior febrile infection starting

TABLE 5-3 Parenteral Drugs for Refractory Status Epilepticus and Special Situations (Infancy, Pregnancy, and Super-refractory Status Epilepticus)^a

Medication	Loading dose (IV, unless specified)	Maintenance dose (IV, unless specified)	Approximate terminal serum $t_{1/2}$ (hours)	Serum level ($\mu\text{g/mL}$) ^b
Adrenocorticotrophic hormone	Older than 2 years = 40-80 U, intramuscularly or subcutaneously Younger than 2 years = 150 U/m ²	Older than 2 years = 40 U intramuscularly per day Younger than 2 years = 75 U/m ² intramuscularly twice a day for 2 weeks	0.25 (intravenously)	Not applicable (NA)
Brivaracetam	Unknown	11-19 kg (24.3-41.9 lb) = 2.5 mg/kg twice a day; 20-49 kg (44.1-108 lb) = 2 mg/kg twice a day; 50+ kg (110.2+ lb) = 100 mg twice a day (age 4+ years); 100 mg twice a day (adult) ^c	9	NA
Ketamine^d	1-2.5 mg/kg	3-10 mg/kg/h ^e	2.5	NA
Lacosamide^f	5-10 mg/kg over 15-30 minutes ^g (US Food and Drug Administration [FDA]-approved "loading dose" is 200 mg in adults)	13 mg/kg/day divided twice a day (children), 200 mg twice a day (adult) ^c	15	4-12
Levetiracetam	60 mg/kg over 15 minutes (maximum 4500 mg)	21 mg/kg twice a day (younger than 6 mo), 25 mg/kg twice a day (6 months to 4 years), 30 mg/kg twice a day (4 to 16 years), 1500 mg twice a day (adult) ^c	7	20-50
Intravenous immunoglobulin (IVIg)	0.4-2 g/kg/day for 3 to 5 days	NA	NA	NA
Magnesium sulfate	50 mg/kg (maximum 4 g)	20-40 mg/kg/h	NA	30-60
Methylprednisolone succinate	10-30 mg/kg/d for 3 to 5 days	Sometimes after 3-5 days, oral prednisone 1 mg/kg/d	NA	NA

CONTINUED ON PAGE 109

between 2 weeks and 24 hours before the onset of refractory status epilepticus with or without fever at the onset of status epilepticus.⁷⁶

NORSE may result from a postinfectious process leading to cerebral inflammation. Other etiologies are autoimmune and paraneoplastic encephalitis (CASE 5-2⁸⁰). CSF often reveals a nonspecific pleocytosis and mildly elevated protein level. A multicenter study that compared patients aged 2 years or older with NORSE and FIRES, other forms of refractory status epilepticus with known etiology, and controls without status epilepticus showed a significant increase of three innate proinflammatory cytokines and chemokines in the serum of the

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Medication	Loading dose (IV, unless specified)	Maintenance dose (IV, unless specified)	Approximate terminal serum $t_{1/2}$ (hours)	Serum level ($\mu\text{g/mL}$) ^b
Midazolam ^h	0.2-0.5 mg/kg	0.1-2.0 mg/kg/h ^e or 2.0-40 $\mu\text{g/kg/min}$	Initially = 1-4.5 (child), 2-7 (adult); Prolonged = up to 24	Variable
Pentobarbital	5-15 mg/kg at maximum rate of 50 mg/min	0.5-5 mg/kg/h ^e	15-22	NA
Propofol ⁱ	1-2 mg/kg bolus every 3-5 minutes up to a maximum of 10 mg/kg	1-15 mg/kg/h initially, then a maximum of 5 mg/kg/h ^e	Initially = 0.67, Prolonged = 4-7, longer than 10 days = 24-72	NA
Pyridoxine	100 mg every 5 minutes. $\times 5$ doses	15-30 mg/kg/d orally or intravenously	NA	NA
Valproic acid	40 mg/kg over 10-60 minutes (maximum up to 20 mg/kg/min)	5-15 mg/kg every 6 hours, starting 30 minutes after the end of loading dose; maximum of 60 mg/kg/d total ^c	9-16	50-150

^a Modified with permission from Vossler DG, et al, *Epilepsy Curr.* ² © 2020 The Author(s).

^b Common steady-state serum concentrations observed in ambulatory epilepsy patients.

^c Maximum FDA-approved maintenance dose for ambulatory patients with epilepsy.

^d Combine with benzodiazepine; avoid in neonates and third trimester of pregnancy.

^e May be titrated to produce burst suppression pattern (5-15 second interburst interval) on continuous EEG monitoring.

^f Atrial arrhythmia, first-, second-, and third-degree heart block, and rarely, ventricular arrhythmia and death have been reported with lacosamide administered orally and parenterally.

^g Theoretical loading dose, but ventricular and atrial arrhythmias are a concern.

^h Clearance is fastest in infants and slows markedly with prolonged administration.

ⁱ In children, avoid or use only briefly because of the risk of propofol infusion syndrome.

CASE 5-1

A 66-year-old man with diabetes, hypertension, hyperlipidemia, and prior right basal ganglia ischemic stroke with left-sided deficits presented to the hospital with 2 days of progressive unresponsiveness and diabetic ketoacidosis. His emergency department glucose level was 542 mg/dL, his pH was 7.25, his HbA_{1c} was greater than 15.5, and his white blood cell count and CSF studies were normal. Noncontrast head CT and MRI revealed age-related atrophy and chronic small vessel ischemic white matter changes (FIGURE 5-1). The CT angiogram was negative.

In the critical care unit, he was afebrile and had sustained left-gaze deviation punctuated by three episodes of right-gaze deviation lasting 30 seconds, each followed by postepisode transient confusion and agitation. His examination revealed lethargy and inattentiveness, but he retained the ability to follow some commands. Status epilepticus and acute toxic-metabolic encephalopathy were diagnosed. Within 1 hour of his third seizure, video-EEG monitoring began. Two hours later, the first of three more focal seizures occurred with rightward adversion of his head and eyes and unresponsiveness. The most clinically prominent seizure involved turning of his head almost 90 degrees to the right with abduction and elevation of the right arm almost in a fencing posture as if he was staring at his hand. The EEG recorded during his fifth seizure after the start of monitoring is shown in FIGURE 5-2 and FIGURE 5-3.

The first 10 episodes on the first day of video-EEG were focal impaired awareness seizures, but after that, all were subclinical (electrographic) seizures. First-phase treatment was a bolus of lorazepam, and second-phase treatment was a 4000 mg bolus of IV levetiracetam. Over the first 5 days of video-EEG, an average of 73 subclinical (electrographic) seizures occurred per day and IV lacosamide and phenytoin were sequentially added to the maintenance levetiracetam. Subclinical (electrographic) seizures stopped on the sixth day of video-EEG. His noncontrast brain MRI on the fourth day is shown in FIGURE 5-1. After a 21-day hospitalization, the patient was discharged at baseline neurologic state taking lacosamide 200 mg twice a day, levetiracetam 1000 mg twice a day, and phenytoin 300 mg nightly.

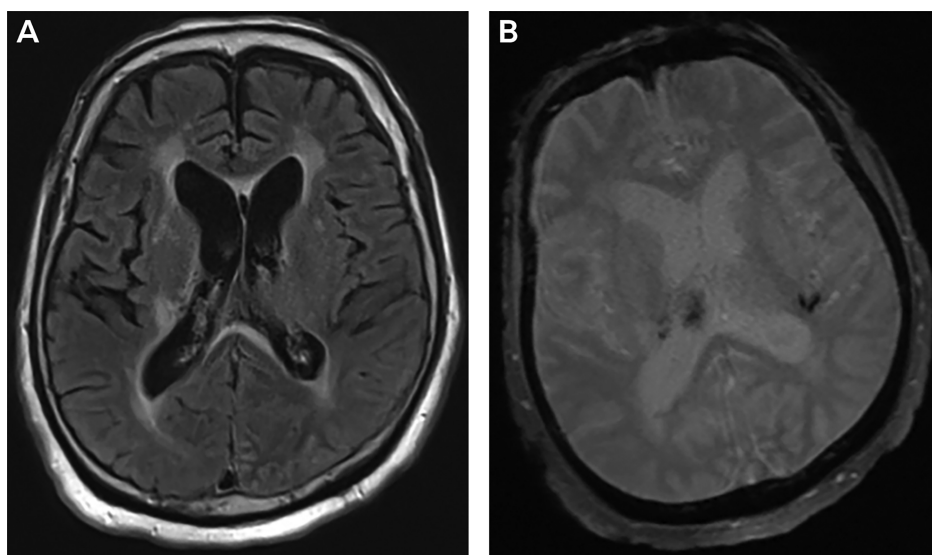


FIGURE 5-1

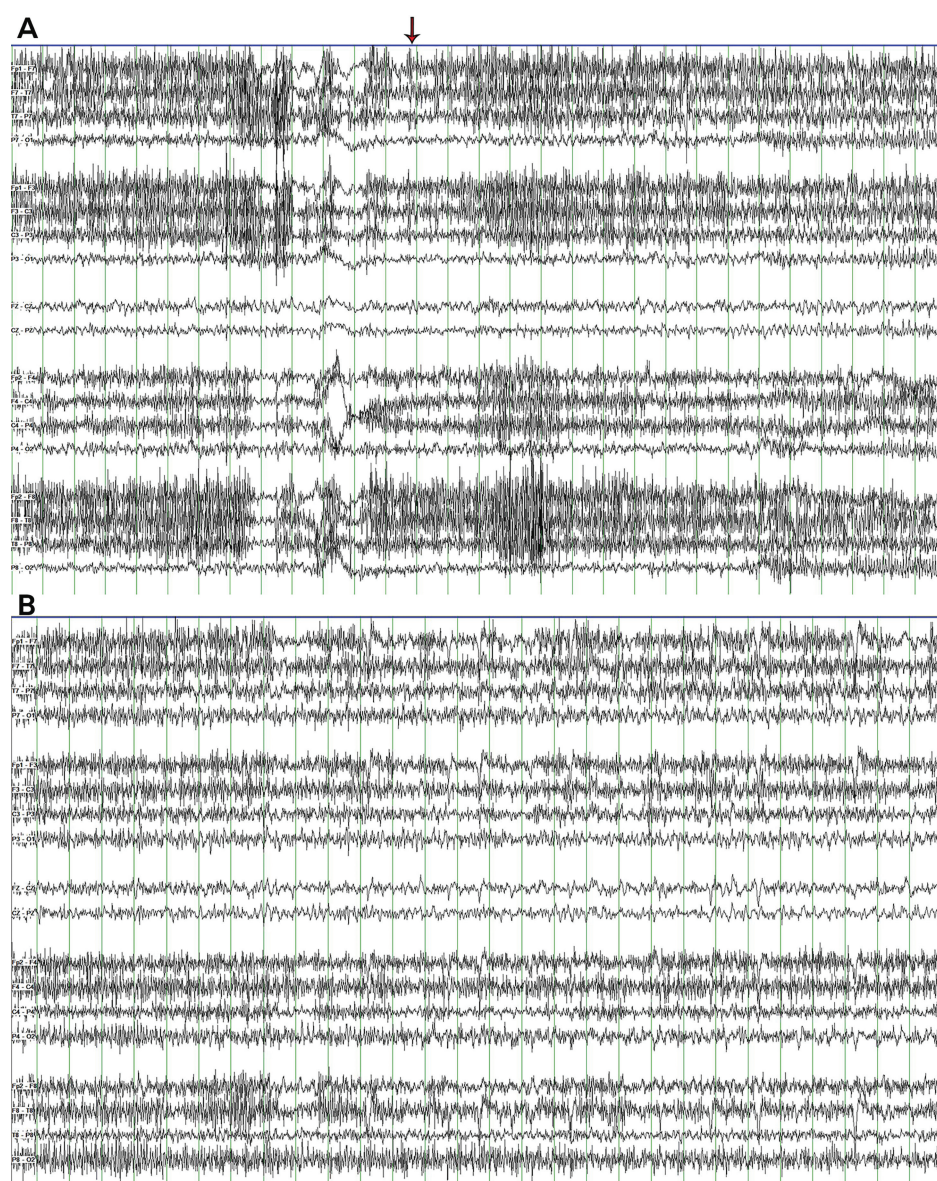
Brain MRI of the patient in **CASE 5-1**. An axial fluid-attenuated inversion recovery (FLAIR) image reveals moderate, presumed chronic, ischemic small vessel disease and an old right posterior frontal periventricular lacunar infarct (A), and an axial gradient-echo image reveals multiple areas of hemosiderin deposition in the left sylvian fissure, right thalamus, and lateral ventricle and subcortical white matter in both temporal, parietal, and occipital lobes (B).

This patient with a depressed level of awareness was initially diagnosed with diabetic ketoacidosis encephalopathy. The clue to the additional diagnosis of nonconvulsive status epilepticus was the observation of repetitive focal impaired awareness seizures without recovery of baseline cognition between them. Nonconvulsive status epilepticus was confirmed by prompt video-EEG monitoring. After the first 10 focal impaired awareness seizures, subclinical seizures persisted for 6 days before cessation, so the EEG was the only biomarker available to inform treatment adjustments. His history of prior stroke ruled out a diagnosis of new-onset refractory status epilepticus (NORSE). Super-refractory status epilepticus was not diagnosed because continuously infused anesthetizing antiseizure medications were not required. This case demonstrates the fairly rapid evolution from individual seizures (developing status epilepticus) to nonconvulsive status epilepticus with focal seizures, then to nonconvulsive status epilepticus with only decreased awareness and subclinical (electrographic) seizures, and finally to refractory status epilepticus. This type of scenario is not uncommon in adults with multiple chronic medical comorbidities who are initially diagnosed with suspected toxic-metabolic encephalopathy. Clinicians should maintain a high index of suspicion of nonconvulsive status epilepticus with these presentations.

COMMENT

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**FIGURE 5-2**

Sequential EEG epochs recorded from the patient in **CASE 5-1**. **A**, The fifth seizure on the first day of video-EEG monitoring revealed the initial ictal discharge over the left hemisphere mixed with substantial muscular artifact during the first 30-second epoch (arrow). **B**, The next 30-second EEG epoch during this seizure is represented. Clinical semiology included sustained rightward head adversion and obtundation. Anteroposterior, longitudinal, bipolar montage; from top to bottom: left temporal, left parasagittal, midline, right parasagittal, right temporal chains.

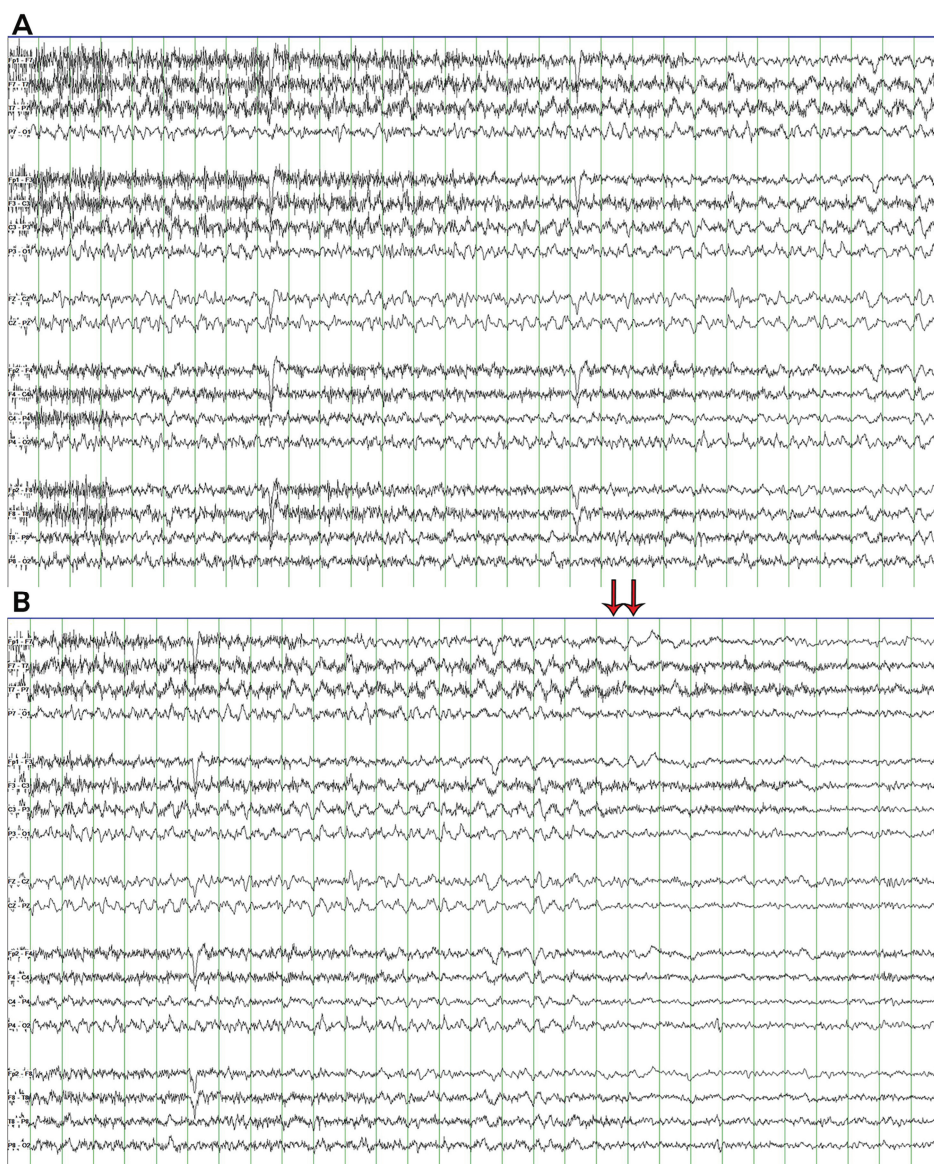


FIGURE 5-3

The third and fourth 30-second EEG epochs recorded during the fifth seizure of the patient in **CASE 5-1**. **A, B**, The ictal discharge evolved from the initial hemispheric 9 Hz alpha frequency waves to 5 Hz to 7 Hz theta waves and spread more widely, left greater than right, and ended 99 seconds after onset (*double arrow*). Anteroposterior, longitudinal, bipolar montage; from top to bottom: left temporal, left parasagittal, midline, right parasagittal, right temporal chains.

CASE 5-2

A 33-year-old woman with chronic asthma experienced 1 week of new afebrile cough, rhinorrhea, and sinus congestion. On her emergency department presentation, she had lethargy, disorientation, incomprehensible language, headache, and blank staring, and she was given 2 mg IV lorazepam for three witnessed episodes of bilateral arm and leg motor seizures. In the emergency department, she was afebrile, had mild leukocytosis with normal differential, normal head CT, and a standard EEG that recorded one subclinical (electrographic) seizure with onset maximally over her left posterior temporal area. Postictally, the patient did not recall a word spoken to her by the technologist during the EEG. Epileptiform (interictal)⁸⁰ discharges appeared maximally over the same left posterior temporal area. She was immediately loaded with a benzodiazepine followed by levetiracetam, but subclinical (electrographic) seizures persisted so video-EEG monitoring was begun. Brain MRI the next day was abnormal (FIGURE 5-4). CSF analysis revealed normal protein and glucose levels, a white blood cell count of 6 cells/mm³ (predominantly neutrophils), normal bacteria culture, and negative test results for herpes simplex virus, varicella-zoster virus, and enterovirus. CSF was sent to a reference laboratory for an autoimmune encephalopathy panel. A 72-hour video-EEG recorded four left posterior temporal area subclinical (electrographic) seizures the first day and persistent arrhythmic delta activity and epileptiform discharges.

The provisional clinical diagnosis was new-onset refractory status epilepticus (NORSE) due to autoimmune encephalitis, so the second treatment was a short course of methylprednisolone, which improved her cognition, aphasia, and seizures. The initial CSF was later reported to contain antineuronal nuclear antibody type 1 (ANNA-1) with a 1:32 titer, so the patient received a 6-month course of cyclophosphamide. Eighteen months after onset, a serum autoimmune epilepsy panel showed ANNA-1 with a 1:1920 titer. Subsequently, the patient had multiple flare-ups of repetitive focal aware seizures with aphasia, each of which were evaluated with inpatient and ambulatory video-EEG sessions that recorded focal left posterior temporal seizures (FIGURE 5-5) with global aphasia, inappropriate laughing, and mostly motionless semiology, and multiple MRI scans revealing waxing and waning findings nearly identical to FIGURE 5-4. Four body positron emission tomography (PET) scans over time were negative for malignancy. She was treated with multiple standard antiseizure medications together in various combinations.

Immunotherapies included rituximab, mycophenolate, and two courses of cyclophosphamide. Treatment with focal cortical resection was deferred because of the risk of aphasia. The patient declined neurostimulator therapy. Five years after onset, seizures were completely controlled with a combination of rituximab, mycophenolate, cenobamate, lacosamide, levetiracetam, pregabalin, and topiramate.

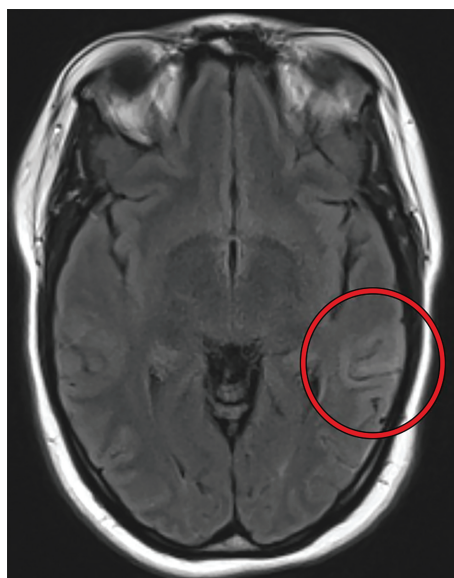


FIGURE 5-4
Brain MRI of the patient in **CASE 5-2**. Axial fluid-attenuated inversion recovery (FLAIR) image reveals focal hyperintense cortical thickening of the left posterior-superior temporal lobe (circle) with no restricted diffusion or enhancement.

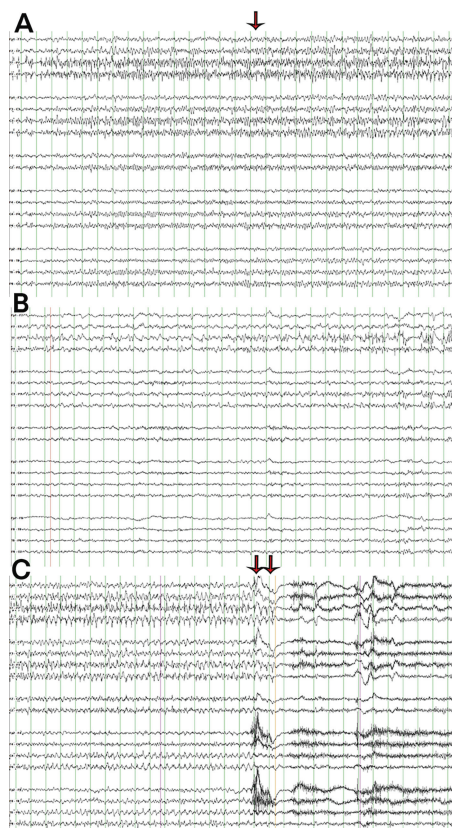


FIGURE 5-5
Three sequential EEG epochs recorded in the patient in **CASE 5-2**. Four years after onset, ambulatory EEG monitoring revealed a subclinical electrographic seizure pattern. The ictal discharge began subtly as focal repetitive spikes over the left posterior temporal area (A, arrow), then evolved to 5 Hz to 7 Hz theta waves that spread more widely left greater than right (B), and ended about 63 seconds after onset (C, arrows). Anteroposterior, longitudinal, bipolar montage; from top to bottom: left temporal, left parasagittal, midline, right parasagittal, right temporal chains.

This is a case of ANNA-1 encephalitis and NORSE, resulting in long-term epilepsy that was initially very refractory to treatment with multiple antiseizure medications and rounds of immunotherapy. Testing failed to reveal a tumor causing paraneoplastic encephalitis. Past antiseizure medications were associated with adverse reactions, including sedation, but the final combination of five antiseizure medications and two immunotherapies were the best tolerated and most effective. Surgical resection carried a risk of neurologic deficit. Vagus nerve stimulation, responsive neurostimulation, deep brain stimulation, and a ketogenic diet remain viable options in this scenario.

COMMENT

patients with NORSE.⁸¹ Brain MRIs demonstrated significantly higher blood-brain barrier permeability in a study of seven adults with NORSE compared with patients with encephalitis without status epilepticus and with healthy controls.⁸² Overall, a 2023 systematic review and meta-analysis of adults (aged 16 years or older) with NORSE determined that the most common etiologies were cryptogenic in 49.9% of patients and autoimmune in 36.2% of patients and that the pooled mortality rate was 22%.⁸³ A 2024 study of well-characterized cases of NORSE found a 19% mortality rate; high rates of subsequent active drug-resistant epilepsy and vocational, cognitive and psychiatric disabilities; and only 4% of patients who experienced full neurologic recovery.⁸⁴

No randomized controlled trials on the treatment of NORSE have been completed to date. One meta-analysis reported that common treatments included antiseizure medications (a median of 5); general anesthesia; immunotherapy, including corticosteroids; IVIg; and plasma exchange.⁸³ International consensus-based recommendations for the treatment of NORSE and FIRES in all age groups were published in 2022.^{85,86} Eighty-five recommendations were developed concerning disease characteristics, diagnostic testing, treatment, and follow-up. Two important recommendations were that immunotherapy should be considered for initiation within 72 hours of onset and that second-line immunotherapy and ketogenic diets should be considered within 7 days after onset in cryptogenic cases.^{85,86} Corticosteroids are often the first-line immunotherapy, and methylprednisolone at a dose of 20 mg/kg to 30 mg/kg (1 g maximum) daily for 3 to 5 days is recommended; IVIg may be given as an alternative.⁸⁵ It is recommended that if a pathogenic antibody is identified or highly suspected, rituximab should be initiated.⁸⁵ In the postacute phase, no specific antiseizure medication is recommended, but if effective in the acute phase, immunomodulation should continue for at least 3 months.⁸⁵

Super-Refractory Status Epilepticus

Super-refractory status epilepticus may be convulsive, but more commonly is nonconvulsive, and is defined as persistent seizures despite more than 24 hours of anesthetizing antiseizure medication use.²⁷ There are myriad etiologies of super-refractory status epilepticus, and they include all of the epilepsies, genetic causes, tumors, trauma, drug-related causes, infections, immune-related causes as well as other categories (including unknown categories) that can cause established status epilepticus, refractory status epilepticus, nonconvulsive status epilepticus, and NORSE.

TREATMENT. The treatment of super-refractory status epilepticus remains challenging and is the subject of a 2021 nonsystematic review.⁸⁷ The review excluded the nonsedating and anesthetizing antiseizure medications covered in the American Epilepsy Society comprehensive review of refractory status epilepticus treatments.² In the super-refractory status epilepticus review, insufficient evidence was found to support that brain surgery, ketogenic diet, inhalation anesthesia, perampanel, pregabalin, lidocaine, or vagus nerve stimulation were effective treatments for super-refractory status epilepticus.⁸⁷ It determined that therapeutic hypothermia was possibly effective in the treatment of adults with super-refractory status epilepticus, but there was insufficient evidence of its effectiveness in neonates with hypoxic-ischemic

encephalopathy.⁸⁷ A new study on the treatment of super-refractory status epilepticus in 91 adults reported a high rate of seizure control but a very low rate of favorable outcome at hospital discharge.⁸⁸

A 2023 systematic review identified 95 articles on nonanoxic super-refractory status epilepticus that included 266 individual patients available for meta-analysis.⁸⁹ These patients had a mean super-refractory status epilepticus duration of 36.3 days and a mean age of 40.8 years.⁸⁵ Acute cerebral events and unknown causes accounted for 41.6% and 22.3% of all etiologies, respectively. At discharge, only 26.8% had zero to slight disability.⁸⁹ In-hospital mortality was 24.1%. Reported mortality depended on the duration of super-refractory status epilepticus up to 28 days. The rate of successful seizure termination continued to increase; however, the proportion of patients with substantial disability also increased significantly with longer durations of super-refractory status epilepticus.⁸⁹ Reported treatment with ketamine, phenobarbital, other barbiturates, vagus nerve stimulator, and ketogenic diet were not associated with improved cessation of status epilepticus or in-hospital survival.⁸⁹

Measurement Tools

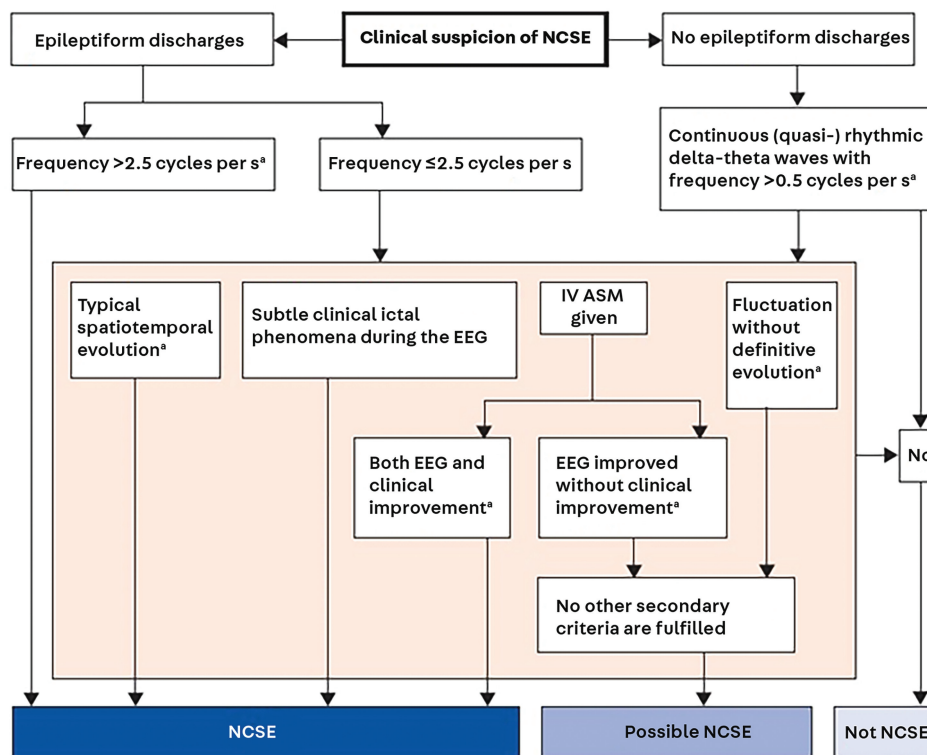
Clinical tests provide objective data to support the management of patients with status epilepticus. Refer to the article “EEG in Epilepsy” by Daniel Weber, DO⁹⁰ in this issue of *Continuum*.

EEG. In addition to the patient’s history and examination, EEG plays a critical role in the diagnosis and management of status epilepticus. Continuous video-EEG monitoring is used to visualize not only the electrophysiologic patterns of tonic-clonic convulsive status epilepticus but more importantly the patterns of nonconvulsive status epilepticus, including focal status epilepticus and nonconvulsive status epilepticus with altered awareness and coma. Interpretation criteria, terminology, and reporting recommendations are available that enhance diagnostic accuracy, inter-rater consistency, and agreement across different health care facilities. Three major guidance documents exist. The first is for general interpretation of EEG: the third edition of a glossary of terms most commonly used by electroencephalographers.⁸⁰ The second is the 2021 version of the American Clinical Neurophysiology’s critical care EEG terminology,⁹¹ which is essential in the care of patients with status epilepticus and also for neurologic critical care diagnoses. More specific are the Salzburg EEG criteria for the diagnosis of nonconvulsive status epilepticus, which have been determined to have high diagnostic accuracy and excellent inter-rater agreement (FIGURE 5-6⁹²).^{92,93}

MRI. Neuroimaging plays an important role not only as a diagnostic test but also as a biomarker of the severity of status epilepticus. New research in 307 patients older than 15 years found peri-ictal MRI abnormalities due to status epilepticus in 26% of patients.⁹⁴ Peri-ictal MRI abnormalities consisted of diffusion-weighted imaging hyperintensities, fluid-attenuated inversion recovery (FLAIR) hyperintensities, and apparent diffusion coefficient signals of varying intensities. The anatomic locations of these peri-ictal MRI abnormalities were cerebral cortex in 75%, thalamus in 61%, and hippocampus and amygdala in 43% of patients.⁹⁴ The patients who had these peri-ictal MRI abnormalities, compared with patients without peri-ictal MRI abnormalities, were significantly more likely to die in the

KEY POINTS

- New-onset refractory status epilepticus (NORSE) is a clinical presentation occurring in patients without active epilepsy or other preexisting relevant neurologic disorders with new onset of refractory status epilepticus without a clear acute or active structural toxic or metabolic cause.
- Febrile infection-related epilepsy syndrome (FIREs), a subcategory of NORSE, is applicable to patients of all ages and requires a prior febrile infection starting between 2 weeks and 24 hours before the onset of refractory status epilepticus with or without fever at the onset of status epilepticus.
- In cryptogenic NORSE, consideration should be given for the initiation of immunotherapy within 72 hours of onset, and second-line immunotherapy and ketogenic diets should be considered within 7 days after onset.
- A 2023 systematic review of nonanoxic super-refractory status epilepticus revealed a mean duration of 36.3 days and a mean age of 40.8 years. Acute cerebral events and unknown etiologies accounted for 41.6% and 22.3% of all etiologies, respectively. In-hospital mortality was 24.1%, and at hospital discharge, only 26.8% had zero to slight disability.

**FIGURE 5-6**

Salzburg EEG criteria for the diagnosis of nonconvulsive status epilepticus. To qualify for a diagnosis of nonconvulsive status epilepticus, the whole EEG recording should be abnormal, and EEG criteria must be continuously present for at least 10 seconds. If criteria are not fulfilled at any stage, EEG recording will not qualify for a diagnosis of nonconvulsive status epilepticus or possible nonconvulsive status epilepticus.

^a Patients with known epileptic encephalopathy should fulfill one of the additional secondary criteria: increase in prominence or frequency of the features above when compared with baseline and observable change in clinical state or improvement of clinical and EEG features with IV antiseizure medications. ASM = antiseizure medication; NCSE = nonconvulsive status epilepticus.

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hospital (27% versus 11%), to have refractory status epilepticus (71% versus 33%), and to have delayed-onset epilepsy (40% versus 21%).⁹⁴ A 2024 study found that peri-ictal MRI abnormalities in the hippocampus and pulvinar of the thalamus were highly specific locations for status epilepticus compared with a control group.⁹⁵

OUTCOME MEASURES. For the prediction of survival of adults with status epilepticus, several prognostic models have been developed. Of them, the Status Epilepticus Severity Score has been the most extensively used to predict, pretreatment, the chance of survival at hospital discharge.⁶⁴ The Status Epilepticus Severity Score relies on four outcome predictors: age, history of seizures, seizure type, and extent of consciousness impairment (TABLE 5-2). The Glasgow Coma Scale is also useful in the prognosis of outcomes in status epilepticus. The age at onset, level of consciousness at admission, and duration of status epilepticus score has been proposed as a predictor of long-term

mortality after status epilepticus.⁹⁶ The age at onset, level of consciousness at admission, and duration of status epilepticus score study found that age, long duration, and nonconvulsive types of status epilepticus in coma were associated with the development of new neurologic deficits, and were predictors of long-term mortality.⁹⁶ One study examined several illness-severity scoring scales and determined that a decreasing Glasgow Coma Scale score and an increasing Status Epilepticus Severity Score had stronger associations with no return to baseline, independent of all other scoring systems.⁹⁷ However, a systematic review and meta-analysis of four different status epilepticus prognostic risk models found that, although Status Epilepticus Severity Score had better discriminative power than one of the models, more research is needed.⁹⁸

For determination of the level of neurologic disability or dependence in activities of daily living, the modified Rankin score is often used in status epilepticus to score both baseline status and outcome at hospital discharge and, rarely, at 3 or more months posthospitalization.

Historically, clinical treatment trials have considered benefits and harms separately, in which a benefit is often considered the primary efficacy endpoint and harms are adverse effects. The Desirability of Outcome Ranking is a method that can simultaneously consider both the benefits and the harms of a treatment. It has been proposed that Desirability of Outcome Ranking methodology be used as a more patient-centric way to conduct status epilepticus clinical trials.⁹⁹

CONCLUSION

There is room to improve certain aspects of clinical practice guidelines in status epilepticus.¹⁰⁰ The newest guidelines and techniques to diagnose, classify, and assess patients with all types of acute seizure emergencies should be fully understood and implemented. Health care providers should adhere to guidelines on treatment. New antiseizure medications and assessment techniques should be incorporated into the approach that health care providers take to address seizure and epilepsy emergencies such as first seizures, acute repetitive seizures, and the several different forms of status epilepticus in children and adults.

REFERENCES

- 1 Glauser T, Shinnar S, Gloss D, et al. Evidence-based guideline: treatment of convulsive status epilepticus in children and adults: report of the guideline committee of the American Epilepsy Society. *Epilepsy Curr* 2016;16(1):48-61. doi:10.5698/1535-7597-16.1.48
- 2 Vossler DG, Bainbridge JL, Boggs JG, et al. Treatment of refractory convulsive status epilepticus: a comprehensive review by the American Epilepsy Society Treatments Committee. *Epilepsy Curr* 2020;20(5):245-264. doi:10.1177/1535759720928269
- 3 Meierkord H, Boon P, Engelsens B, et al. EFNS guideline on the management of status epilepticus in adults. *European Journal of Neurology* 2010;17(3):348-355. doi:10.1111/j.1468-1331.2009.02917.x
- 4 Brophy GM, Bell R, Claassen J, et al. Guidelines for the evaluation and management of status epilepticus. *Neurocrit Care* 2012;17(1):3-23. doi:10.1007/s12028-012-9695-z
- 5 Treatment of convulsive status epilepticus: recommendations of the Epilepsy Foundation of America's working group on status epilepticus. *JAMA* 1993;270(7):854-859.

KEY POINTS

- Continuous video-EEG monitoring is used to visualize not only the electrophysiologic patterns of tonic-clonic convulsive status epilepticus but more importantly the patterns of focal status epilepticus and nonconvulsive status epilepticus with altered awareness and coma.

- Peri-ictal MRI abnormalities including diffusion-weighted, fluid-attenuated inversion recovery (FLAIR), and apparent diffusion coefficient signal abnormalities occur in one-fourth of patients with status epilepticus.

- In one study, peri-ictal MRI abnormalities were found in the cerebral cortex in 75%, thalamus in 61%, and hippocampus and amygdala in 43% of patients with status epilepticus.

- 6 McTague A, Martland T, Appleton R. Drug management for acute tonic-clonic convulsions including convulsive status epilepticus in children. *Cochrane Database Syst Rev* 2018;1(1): CD001905. doi:10.1002/14651858.CD001905.pub3
- 7 Pang EW, Lawn ND, Lee J, Dunne JW. Mortality after a first-ever unprovoked seizure. *Epilepsia* 2023;64(5):1266-1277. doi:10.1111/epi.17567
- 8 Shinnar S, Berg AT, Moshe SL, et al. The risk of seizure recurrence after a first unprovoked afebrile seizure in childhood: an extended follow-up. *Pediatrics* 1996;98(2 Pt 1):216-225.
- 9 Shinnar S, Berg AT, O'Dell C, et al. Predictors of multiple seizures in a cohort of children prospectively followed from the time of their first unprovoked seizure. *Ann Neurol* 2000;48(2): 140-147.
- 10 Shinnar S, Berg AT, Moshe SL, Shinnar R. How long do new-onset seizures in children last? *Ann Neurol* 2001;49(5):659-664.
- 11 Camfield P, Camfield C, Dooley J, Smith E, Garner B. A randomized study of carbamazepine versus no medication after a first unprovoked seizure in childhood. *Neurology* 1989;39(6):851-852. doi:10.1212/wnl.39.6.851
- 12 Randomized clinical trial on the efficacy of antiepileptic drugs in reducing the risk of relapse after a first unprovoked tonic-clonic seizure. First Seizure Trial Group (FIR.S.T. Group). *Neurology* 1993;43(3 Pt 1):478-483. doi:10.1212/wnl.43.3.part_1.478
- 13 Gilad R, Lampl Y, Gabbay U, Eshel Y, Sarova-Pinhas I. Early treatment of a single generalized tonic-clonic seizure to prevent recurrence. *Arch Neurol* 1996;53(11):1149-1152. doi:10.1001/archneur.1996.00550110089017
- 14 Hirtz D, Ashwal S, Berg A, et al. Practice parameter: evaluating a first nonfebrile seizure in children: report of the quality standards subcommittee of the American Academy of Neurology, the Child Neurology Society, and the American Epilepsy Society. *Neurology* 2000; 55(5):616-623. doi:10.1212/wnl.55.5.616
- 15 Hirtz D, Berg A, Bettis D, et al. Practice parameter: treatment of the child with a first unprovoked seizure: report of the Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society. *Neurology* 2003;60(2):166-175. doi:10.1212/01.wnl.0000033622.27961.b6
- 16 Krumholz A, Wiebe S, Gronseth GS, et al. Evidence-based guideline: management of an unprovoked first seizure in adults: report of the Guideline Development Subcommittee of the American Academy of Neurology and the American Epilepsy Society. *Neurology* 2015;84(16):1705-1713. doi:10.1212/WNL.0000000000001487
- 17 Marson A, Jacoby A, Johnson A, et al. Immediate versus deferred antiepileptic drug treatment for early epilepsy and single seizures: a randomised controlled trial. *Lancet* 2005;365(9476): 2007-2013. doi:10.1016/S0140-6736(05)66694-9
- 18 Chandra B. First seizure in adults: to treat or not to treat. *Clin Neurol Neurosurg* 1992;94 Suppl: S61-63. doi:10.1016/0303-8467(92)90024-w
- 19 Ruggles KH, Haessly SM, Berg RL. Prospective study of seizures in the elderly in the Marshfield Epidemiologic Study Area (MESA). *Epilepsia* 2001;42(12):1594-1599. doi:10.1046/j.1528-1157.2001.35900.x
- 20 Lawn ND, Pang EW, Lee J, Dunne JW. First seizure from sleep: clinical features and prognosis. *Epilepsia* 2023;64(10):2714-2724. doi:10.1111/epi.17712
- 21 De Stefano P, Ménétré E, Stancu P, et al. Added value of advanced workup after the first seizure: a 7-year cohort study. *Epilepsia* 2023;64(12): 3246-3256. doi:10.1111/epi.17771
- 22 Bao EL, Chao LY, Ni P, et al. Antiepileptic drug treatment after an unprovoked first seizure: a decision analysis. *Neurology* 2018;91(15): e1429-e1439. doi:10.1212/WNL.0000000000006319
- 23 Vossler DG, Marcuse LV. Measuring treatment response in the epilepsy clinic. In: Engel Jr. J, Moshé SL, editors. *Epilepsy: A Comprehensive Textbook*. 3rd ed. Lippincott Williams & Wilkins (LWW); 2023:1398-1410.
- 24 Wilson JV, Reynolds EH. Texts and documents. Translation and analysis of a cuneiform text forming part of a Babylonian treatise on epilepsy. *Medical History* 1990;34(2):185. doi:10.1017/s0025727300050651
- 25 Meldrum BS. Historical overview. In: Wasterlain CG, Treiman DM, Meldrum BS, editors. *Status Epilepticus: Mechanisms and Management*. MIT Press; 2006:3-9.
- 26 Trinka E, Cock H, Hesdorffer D, et al. A definition and classification of status epilepticus-report of the ILAE Task Force on classification of status epilepticus. *Epilepsia* 2015;56(10):1515-1523. doi:10.1111/epi.13121
- 27 Shorvon S, Ferlisi M. The treatment of super-refractory status epilepticus: a critical review of available therapies and a clinical treatment protocol. *Brain* 2011;134(Pt 10):2802-2818. doi:10.1093/brain/awr215
- 28 Gronseth GS, Cox J, Gloss D, et al. Clinical practice guideline process manual. Published online 2017. aan.com/siteassets/home-page/policy-and-guidelines/guidelines/about-guidelines/17guidelineprocman_pg.pdf. Accessed November 25, 2024.

- 29 Silbergleit R, Durkalski V, Lowenstein D, et al. Intramuscular versus intravenous therapy for prehospital status epilepticus. *N Engl J Med* 2012; 366(7):591-600. doi:10.1056/NEJMoa1107494
- 30 Alldredge BK, Gelb AM, Isaacs SM, et al. A comparison of lorazepam, diazepam, and placebo for the treatment of out-of-hospital status epilepticus. *N Engl J Med* 2001;345(9): 631-637. doi:10.1056/NEJMoa002141
- 31 Treiman DM, Meyers PD, Walton NY, et al. A comparison of four treatments for generalized convulsive status epilepticus. Veterans Affairs status epilepticus cooperative study group. *N Engl J Med* 1998;339(12):792-798. doi:10.1056/NEJM199809173391202
- 32 Cruickshank M, Imamura M, Booth C, et al. Pre-hospital and emergency department treatment of convulsive status epilepticus in adults: an evidence synthesis. *Health Technol Assess* 2022;26(20):1-76. doi:10.3310/RSVK2062
- 33 Leppik IE, Derivan AT, Homan RW, et al. Double-blind study of lorazepam and diazepam in status epilepticus. *JAMA* 1983;249(11):1452-1454.
- 34 Walker JE, Homan RW, Vasko MR, et al. Lorazepam in status epilepticus. *Ann Neurol* 1979; 6(3):207-213. doi:10.1002/ana.410060305
- 35 Guterman EL, Burke JF, Sporer KA. Prehospital treatment of status epilepticus in the United States. *JAMA* 2021;326(19):1970-1971. doi:10.1001/jama.2021.15964
- 36 Guterman EL, Sanford JK, Betjemann JP, et al. Prehospital midazolam use and outcomes among patients with out-of-hospital status epilepticus. *Neurology* 2020;95(24):e3203-e3212. doi:10.1212/WNL.0000000000010913
- 37 Kellinghaus C, Rossetti AO, Trinka E, et al. Factors predicting cessation of status epilepticus in clinical practice: data from a prospective observational registry (SENSE). *Ann Neurol* 2019; 85(3):421-432. doi:10.1002/ana.25416
- 38 Sathe AG, Underwood E, Coles LD, et al. Patterns of benzodiazepine underdosing in the established status epilepticus treatment trial. *Epilepsia* 2021;62(3):795-806. doi:10.1111/epi.16825
- 39 Beuchat I, Rosenow F, Kellinghaus C, et al. Refractory status epilepticus: risk factors and analysis of intubation in the multicenter SENSE registry. *Neurology* 2022;99(16):e1824-e1834. doi:10.1212/WNL.00000000000201099
- 40 Fong MWK, Stephens E, Brockington A, et al. Status epilepticus in Auckland, New Zealand: Treatment patterns and determinants of outcome in a prospective population-based cohort. *Epilepsia* 2024;65(6):1605-1619. doi:10.1111/epi.17975
- 41 Gaínza-Lein M, Sánchez Fernández I, Jackson M, et al. Association of time to treatment with short-term outcomes for pediatric patients with refractory convulsive status epilepticus. *JAMA Neurol* 2018;75(4):410-418. doi:10.1001/jamaneurol.2017.4382
- 42 Sánchez Fernández I, Gaínza-Lein M, Abend NS, et al. Factors associated with treatment delays in pediatric refractory convulsive status epilepticus. *Neurology* 2018;90(19):e1692-e1701. doi:10.1212/WNL.00000000000005488
- 43 Sánchez Fernández I, Abend NS, Agadi S, et al. Time from convulsive status epilepticus onset to anticonvulsant administration in children. *Neurology* 2015;84(23):2304-2311. doi:10.1212/WNL.00000000000001673
- 44 Vidaurre J, Albert DVF, Parker W, et al. Improving time for administration of second-line antiseizure medications for children with generalized convulsive status epilepticus using quality improvement methodology. *Epilepsia* 2021;62(10):2496-2504. doi:10.1111/epi.17026
- 45 Fesler JR, Belcher AE, Moosa AN, et al. The efficacy and use of a pocket card algorithm in status epilepticus treatment. *Neurol Clin Pract* 2021;11(5):406-412. doi:10.1212/CPJ.0000000000000922
- 46 Kapur J, Elm J, Chamberlain JM, et al. Randomized trial of three anticonvulsant medications for status epilepticus. *N Engl J Med* 2019;381(22): 2103-2113. doi:10.1056/NEJMoa1905795
- 47 Navarro V, Dagron C, Elie C, et al. Prehospital treatment with levetiracetam plus clonazepam or placebo plus clonazepam in status epilepticus (SAMUKeppra): a randomised, double-blind, phase 3 trial. *Lancet Neurol* 2016;15(1):47-55. doi:10.1016/S1474-4422(15)00296-3
- 48 Nene D, Mundlamuri RC, Satishchandra P, et al. Comparing the efficacy of sodium valproate and levetiracetam following initial lorazepam in elderly patients with generalized convulsive status epilepticus (GCSE): a prospective randomized controlled pilot study. *Seizure* 2019; 65:111-117. doi:10.1016/j.seizure.2019.01.015
- 49 Lyttle MD, Rainford NEA, Gamble C, et al. Levetiracetam versus phenytoin for second-line treatment of paediatric convulsive status epilepticus (EcLiPSE): a multicentre, open-label, randomised trial. *Lancet* 2019;393(10186): 2125-2134. doi:10.1016/S0140-6736(19)30724-X
- 50 Dalziel SR, Borland ML, Furey J, et al. Levetiracetam versus phenytoin for second-line treatment of convulsive status epilepticus in children (ConSEPT): an open-label, multicentre, randomised controlled trial. *Lancet* 2019; 393(10186):2135-2145. doi:10.1016/S0140-6736(19) 30722-6
- 51 Khajeh A, Yaghoubinia F, Yaghoubi S, Fayyazi A, Miri Aliabad G. Comparison of the effect of phenobarbital versus sodium valproate in management of children with status epilepticus. *Iran J Child Neurol* 2018;12(4):85-93.

- 52 Su Y, Huang H, Jiang M, et al. Phenobarbital versus valproate for generalized convulsive status epilepticus in adults (2): a multicenter prospective randomized controlled trial in China (China 2-P vs. V). *Epilepsy Res* 2021;177:106755. doi:10.1016/j.eplesyres.2021.106755
- 53 Nakamura K, Marushima A, Takahashi Y, et al. Levetiracetam versus fosphenytoin as a second-line treatment after diazepam for adult convulsive status epilepticus: a multicentre non-inferiority randomised control trial. *J Neurol Neurosurg Psychiatry* 2023;94(1):42-48. doi:10.1136/jnnp-2022-329485
- 54 Mayer SA, Claassen J, Lokin J, et al. Refractory status epilepticus: frequency, risk factors, and impact on outcome. *Arch Neurol* 2002;59(2):205-210. doi:10.1001/archneur.59.2.205
- 55 Holtkamp M, Othman J, Buchheim K, Meierkord H. Predictors and prognosis of refractory status epilepticus treated in a neurological intensive care unit. *J Neurol Neurosurg Psychiatry* 2005;76(4):534-539. doi:10.1136/jnnp.2004.041947
- 56 Mundlamuri RC, Sinha S, Subbakrishna DK, et al. Management of generalised convulsive status epilepticus (SE): a prospective randomised controlled study of combined treatment with intravenous lorazepam with either phenytoin, sodium valproate or levetiracetam-pilot study. *Epilepsy Res* 2015;114:52-58. doi:10.1016/j.eplesyres.2015.04.013
- 57 Beuchat I, Novy J, Rosenow F, et al. Staged treatment response in status epilepticus: lessons from the SENSE registry. *Epilepsia* 2024;65(2):338-349. doi:10.1111/epi.17817
- 58 Novy J, Logroscino G, Rossetti AO. Refractory status epilepticus: a prospective observational study. *Epilepsia* 2010;51(2):251-256. doi:10.1111/j.1528-1167.2009.02323.x
- 59 Rossetti AO, Logroscino G, Bromfield EB. Refractory status epilepticus: effect of treatment aggressiveness on prognosis. *Arch Neurol* 2005;62(11):1698-1702. doi:10.1001/archneur.62.11.1698
- 60 Choi SA, Lee H, Kim K, et al. Mortality, disability, and prognostic factors of status epilepticus: a nationwide population-based retrospective cohort study. *Neurology* 2022;99(13):e1393-e1401. doi:10.1212/WNL.0000000000200912
- 61 Sutter R, Marsch S, Fuhr P, Kaplan PW, Rüegg S. Anesthetic drugs in status epilepticus: risk or rescue? a 6-year cohort study. *Neurology* 2014;82(8):656-664. doi:10.1212/WNL.000000000000009
- 62 Marchi NA, Novy J, Faouzi M, et al. Status epilepticus: impact of therapeutic coma on outcome. *Crit Care Med* 2015;43(5):1003-1009. doi:10.1097/CCM.0000000000000881
- 63 Alvarez V, Lee JW, Westover MB, et al. Therapeutic coma for status epilepticus: differing practices in a prospective multicenter study. *Neurology* 2016;87(16):1650-1659. doi:10.1212/WNL.0000000000003224
- 64 Rossetti AO, Logroscino G, Milligan TA, et al. Status Epilepticus Severity Score (STESS): a tool to orient early treatment strategy. *J Neurol* 2008;255(10):1561-1566. doi:10.1007/s00415-008-0989-1
- 65 Muhlhofer WG, Layfield S, Lowenstein D, et al. Duration of therapeutic coma and outcome of refractory status epilepticus. *Epilepsia* 2019;60(5):921-934. doi:10.1111/epi.14706
- 66 De Stefano P, Baumann SM, Semmlack S, et al. Safety and efficacy of coma induction following first-line treatment in status epilepticus: a 2-center study. *Neurology* 2021;97(6):e564-e576. doi:10.1212/WNL.0000000000012292
- 67 Fisch U, Jünger AL, Baumann SM, et al. Association between dose escalation of anesthetics and outcomes in patients with refractory status epilepticus. *Neurology* 2024;102(2):e207995. doi:10.1212/WNL.0000000000207995
- 68 Au YK, Kananah MF, Rahangdale R, et al. Treatment of refractory status epilepticus with continuous intravenous anesthetic drugs: a systematic review. *JAMA Neurol* 2024;81(5):534-548. doi:10.1001/jamaneurol.2024.0108
- 69 De Stefano P, Baumann SM, Grzonka P, et al. Early timing of anesthesia in status epilepticus is associated with complete recovery: a 7-year retrospective two-center study. *Epilepsia* 2023;64(6):1493-1506. doi:10.1111/epi.17614
- 70 Chiu WT, Campozano V, Schiefecker A, et al. Management of refractory status epilepticus: an international cohort study (MORSE CODE) analysis of patients managed in the ICU. *Neurology* 2022;99(11):e1191-e1201. doi:10.1212/WNL.0000000000200818
- 71 Jacobowitz M, Mulvihill C, Kaufman MC, et al. Ketamine for management of neonatal and pediatric refractory status epilepticus. *Neurology* 2022;99(12):e1227-e1238. doi:10.1212/WNL.0000000000200889
- 72 Chiriboga N, Spentzas T, Abu-Sawwa R. A systematic review and meta-analysis of ketamine in pediatric status epilepticus. *Epilepsia* 2024;65(8):2200-2212. doi:10.1111/epi.18035
- 73 Semmlack S, Yeginsoy D, Spiegel R, et al. Emergency response to out-of-hospital status epilepticus: a 10-year observational cohort study. *Neurology* 2017;89(4):376-384. doi:10.1212/WNL.0000000000004147
- 74 Shneker BF, Fountain NB. Assessment of acute morbidity and mortality in nonconvulsive status epilepticus. *Neurology* 2003;61(8):1066-1073. doi:10.1212/01.wnl.0000082653.40257.0b

- 75 Gaspard N, Foreman BP, Alvarez V, et al. New-onset refractory status epilepticus: etiology, clinical features, and outcome. *Neurology* 2015;85(18):1604-1613. doi:10.1212/WNL.0000000000001940
- 76 Hirsch LJ, Gaspard N, van Baalen A, et al. Proposed consensus definitions for new-onset refractory status epilepticus (NORSE), febrile infection-related epilepsy syndrome (FIRES), and related conditions. *Epilepsia* 2018;59(4):739-744. doi:10.1111/epi.14016
- 77 Gaspard N, Hirsch LJ, Sculier C, et al. New-onset refractory status epilepticus (NORSE) and febrile infection-related epilepsy syndrome (FIRES): state of the art and perspectives. *Epilepsia* 2018; 59(4):745-752. doi:10.1111/epi.14022
- 78 Sculier C, Barcia Aguilar C, Gaspard N, et al. Clinical presentation of new onset refractory status epilepticus in children (the pSERG cohort). *Epilepsia* 2021;62(7):1629-1642. doi:10.1111/epi.16950
- 79 Matthews E, Alkhachroum A, Massad N, et al. New-onset super-refractory status epilepticus: a case series of 26 patients. *Neurology* 2020;95(16):e2280-e2285. doi:10.1212/WNL.00000000000010787
- 80 Kane N, Acharya J, Beniczky S, et al. A revised glossary of terms most commonly used by clinical electroencephalographers and updated proposal for the report format of the EEG findings. Revision 2017. *Clin Neurophysiol Pract* 2017;2:170-185. doi:10.1016/j.cnp.2017.07.002
- 81 Hanin A, Cespedes J, Dorgham K, et al. Cytokines in new-onset refractory status epilepticus predict outcomes. *Ann Neurol* 2023;94(1):75-90. doi:10.1002/ana.26627
- 82 Li H, Liu X, Wang R, et al. Blood-brain barrier damage and new onset refractory status epilepticus: an exploratory study using dynamic contrast-enhanced magnetic resonance imaging. *Epilepsia* 2023;64(6):1594-1604. doi:10.1111/epi.17576
- 83 Tharmaraja T, Ho JSY, Neligan A, Rajakulendran S. The etiology and mortality of new-onset refractory status epilepticus (NORSE) in adults: a systematic review and meta-analysis. *Epilepsia* 2023;64(5):1113-1124. doi:10.1111/epi.17523
- 84 Costello DJ, Matthews E, Aurangzeb S, et al. Clinical outcomes among initial survivors of cryptogenic new-onset refractory status epilepticus (NORSE). *Epilepsia* 2024;65(6):1581-1588. doi:10.1111/epi.17950
- 85 Wickstrom R, Taraschenko O, Dilella R, et al. International consensus recommendations for management of new onset refractory status epilepticus (NORSE) including febrile infection-related epilepsy syndrome (FIRES): summary and clinical tools. *Epilepsia* 2022;63(11):2827-2839. doi:10.1111/epi.17391
- 86 Wickstrom R, Taraschenko O, Dilella R, et al. International consensus recommendations for management of new onset refractory status epilepticus (NORSE) incl. febrile infection-related epilepsy syndrome (FIRES): statements and supporting evidence. *Epilepsia* 2022;63(11): 2840-2864. doi:10.1111/epi.17397
- 87 Ochoa JG, Dougherty M, Papanastassiou A, et al. Treatment of super-refractory status epilepticus: a review. *Epilepsy Curr* 2021;21(6): 1535759721999670. doi:10.1177/1535759721999670
- 88 Kunst S, Rojo M, Schmidbauer ML, et al. Phenobarbital in super-refractory status epilepticus (PIRATE): a retrospective, multicenter analysis. *Epilepsia* 2023;64(6):1482-1492. doi:10.1111/epi.17608
- 89 Cornwall CD, Krøigård T, Kristensen JSS, Callesen HE, Beier CP. Outcomes and treatment approaches for super-refractory status epilepticus: a systematic review and meta-analysis. *JAMA Neurol* 2023;80(9):959-968. doi:10.1001/jamaneurol.2023.2407
- 90 Weber D. EEG in Epilepsy. *Continuum (Minneapolis)* 2025;31(1, Epilepsy):38-60.
- 91 Hirsch LJ, Fong MWK, Leitinger M, et al. American Clinical Neurophysiology Society's standardized critical care EEG terminology: 2021 version. *J Clin Neurophysiol* 2021;38(1):1-29. doi:10.1097/WNP.0000000000000806
- 92 Leitinger M, Trinka E, Gardella E, et al. Diagnostic accuracy of the Salzburg EEG criteria for non-convulsive status epilepticus: a retrospective study. *Lancet Neurol* 2016;15(10):1054-1062. doi:10.1016/S1474-4422(16)30137-5
- 93 Leitinger M, Beniczky S, Rohrer A, et al. Salzburg consensus criteria for non-convulsive status epilepticus-approach to clinical application. *Epilepsy Behav* 2015;49:158-163. doi:10.1016/j.yebeh.2015.05.007
- 94 Bonduelle T, Ollivier M, Trin K, et al. Association of peri-ictal MRI abnormalities with mortality, antiseizure medication refractoriness, and morbidity in status epilepticus. *Neurology* 2023;100(9):e943-e953. doi:10.1212/WNL.0000000000001599
- 95 Bosque Varela P, Tabaei Damavandi P, Machegger L, et al. Magnetic resonance imaging fingerprints of status epilepticus: A case-control study. *Epilepsia* 2024;65(6):1620-1630. doi:10.1111/epi.17949
- 96 Roberg LE, Monsson O, Kristensen SB, et al. Prediction of long-term survival after status epilepticus using the ACD score. *JAMA Neurol* 2022;79(6):604-613. doi:10.1001/jamaneurol.2022.0609
- 97 Semmlack S, Kaplan PW, Spiegel R, et al. Illness severity scoring in status epilepticus-when STESS meets APACHE II, SAPS II, and SOFA. *Epilepsia* 2019;60(2):189-200. doi:10.1111/epi.14623

- 98 Yuan F, Damien C, Gaspard N. Prognostic scores in status epilepticus: a systematic review and meta-analysis. *Epilepsia* 2023;64(1):17-28. doi:10.1111/epi.17442
- 99 Chamberlain JM, Kapur J, Silbergleit RS, et al. Desirability of outcome ranking for status epilepticus: a benefit-risk approach to design and analyses of clinical SE trials. *Neurology* 2023;101(16):e1633-e1639. doi:10.1212/WNL.0000000000207684
- 100 Vignatelli L, Tontini V, Meletti S, et al. Clinical practice guidelines on the management of status epilepticus in adults: a systematic review. *Epilepsia* 2024;65(6):1512-1530. doi:10.1111/epi.17982

DISCLOSURE

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